SURGERY
GYNECOLOGY AND OBSTETRICS
An International Magazine, Published Monthly

VOLUME 66 APRIL, 1938 NUMBER 4

INTUBATION STUDIES OF THE HUMAN SMALL INTESTINE

X. A Non-Surgical Method of Treating, Localizing and Diagnosing the Nature of Obstructive Lesions

W. OSLER ABBOTT, M.D., Philadelphia, Pennsylvania, CHARLES G. JOHNSTON, M.D., F.A.C.S., Detroit, Michigan

SINCE the decline in the incidence of typhoid fever, intestinal obstruction has become the most lethal affection of the small bowel. Its local treatment consists of (1) reducing the distention of the gut proximal to the lesion, (2) locating and relieving the obstruction, and (3) excising any gangrenous tissue devitalized by a disturbance of its blood supply. Until recently operation was relied upon to accomplish these three ends, but the mortality in cases so handled has always been high. The studies of Wangensteen and Paine, however, have most clearly brought out the facts (a) that deflation of the stomach and, if possible, of the duodenum will often decompress the proximal small intestine, with a reduction in the mortality incident to subsequent operation, and (b) that, when the obstruction is due to kinking by adhesions and perpetuated by the distention itself, it may be permanently relieved by decompression alone. However, a fairly large group of patients with obstruction remains in which gastroduodenal suction is not enough to relieve the distention and a still larger group in which, though the distention be relieved, the location, as well as the nature, of the obstructive lesion is still unknown. It is for these cases that we now offer a method of management that will often decompress the abdomen by completely emptying the entire small intestine proximal to the obstruction, and that has, in certain cases, enabled a restitution of normal intestinal action to occur without the necessity of surgical intervention. Moreover, having advanced the tube to the point of obstruction, it often becomes possible by the study of aspirated intestinal contents and by the injection of a minimal amount of an opaque medium through the tube to identify both the position and the nature of the obstructing lesion. Thus two of the three objectives of surgery may be met, but it can not be too strongly emphasized that the third indication remains and that whenever gangrene of the gut is suspected operation must continue to be the treatment of immediate choice.

From the Gastro-Intestinal Section, Kinsey-Thomas Foundation of the Medical Clinic, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, and the Department of Surgery, Wayne University College of Medicine and Receiving Hospital, Detroit, Michigan.

Aided by a grant from the Committee on Scientific Research of the American Medical Association.

Dr. Abbott, H. F. M. Kirby, Fellow in Surgical Physiology.

METHOD

The procedure is based on the method described by Miller and Abbott for intubation of the small intestine. For the relief of intestinal obstruction it is best carried out as follows: The patient is lifted to a litter and brought to a fluoroscopic room. The litter mattress with the patient on it is slid upon the fluoroscopic table. A No. 14 or No. 16 F. duodenal tube with a No. 3 F. rubber tube lightly tied to it is passed in through the patient's nose and out at his mouth. On the end of the larger tube is tied a duodenal bucket and on the end of the fine tube stiffened by a centimeter length of small brass tubing is tied a thin rubber balloon which, when inflated, holds 50 cubic centimeters of air. The collapsed balloon is tied beside the tip of the larger tube, and then the distal end of the apparatus is drawn back into the patient's pharynx and swallowed. When the duodenal bucket can be seen by the fluoroscope to have reached the mid-duodenum, a volume of about 30 cubic centimeters of air is injected into the balloon while constant suction is maintained on the larger tube. As the gas and fluid are sucked out of the gut, the intestinal walls contract and, regaining their normal propulsive movement, they force the balloon ahead. The suction likewise collapses the intestine, loop by loop, as the tip of the tube advances until the obstruction is reached, by which time relief of distention and with it relief of pain have occurred. In some instances no other treatment is necessary.

Variations in the apparatus are occasionally desirable. Our standard two lumen tube[1] has been used at times but has proved too large and stiff to be passed with ease through the nose of an average patient. The ideal tube should have two lumina, one very large for the aspiration of intestinal contents and one very small for the introduction of air into the balloon. Such a tube has just been devised for us and is proving satisfactory.[2]

Variations in the method of passing the tube have been used. In many individuals the nose will permit the passage of the tube with the balloon and a Twiss duodenal tip already attached. When fluoroscopic control seems inadvisable, as is often the case, the tube may be started according to the usual routine for passing any duodenal tube, the balloon being inflated when characteristic duodenal contents begin to flow. If for any reason the patient can not be rolled on his right side to let the bucket "sink" to the pylorus, he may be rolled on his left side and sufficient air placed in the balloon to "float" it to the pylorus. When this is attempted the stomach must first be emptied as air in the stomach will prevent the balloon from "floating," otherwise suction should be deferred until the tube has entered the duodenum as the pylorus is often dilated together with the stomach and so may be more easily traversed before than after deflation has been accomplished.

In the cases in which an organic obstruction is suspected, diagnostic measures may now be undertaken. The injection of a small amount of barium sulphate in dilute suspension will frequently indicate the point of constriction and the pattern of the intestinal mucosa. The examination of the aspirated contents for blood further aids in distinguishing intrinsic lesions involving the mucosa from extrinsic lesions, such as adhesions which have obstructed the lumen by pressure from without. Manometric determinations of the pressure exerted by the intestinal wall upon the balloon give further indication of the element of spasm involved.

Having deflated the gut and, if possible, identified the obstruction by barium injection and study of the intestinal contents, one may leave the apparatus in place for days with constant or intermittent suction. If function has been restored, the tube may still be left in place, without suction being applied, to meet further emergencies should they arise. Otherwise the balloon should be deflated and, with gentle traction, the tube may be pulled backward through the small gut and stomach, even though the tip had reached the ileocecal valve. The longest time required for the withdrawal of 10 feet of tubing in our experience has been 15 minutes; ordinarily 10 minutes suffice.

In a normal individual the apparatus will advance along the intestine at the rate of about 1 centimeter per minute or 2 feet an

[1] U. S. Rubber Products Co., Passaic, New Jersey.
[2] Lee Tire and Rubber Co., Conshohocken, Pennsylvania.

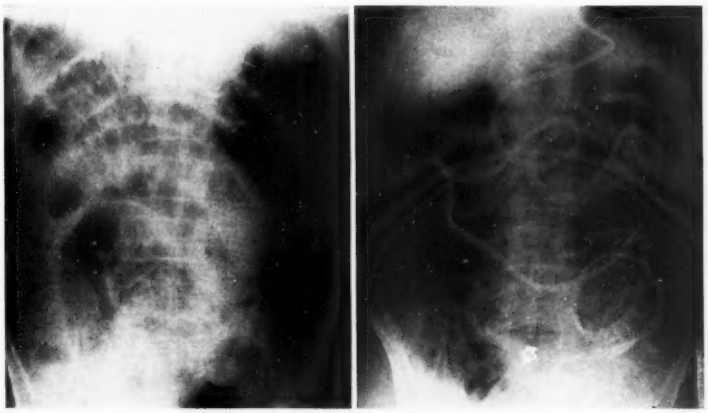


Fig. 1. Paralytic ileus. Case 3, F.F. a, left, Small intestinal distention 4 days after operation. b, Decompression of the intestinal tract by the passage of a No. 14 F. tube for aspiration fastened to a No. 3 F. tube bearing an air-filled balloon.

hour. A length of 6 to 8 feet of tubing is generally enough to reach from the pylorus to the cecum (8 to 10 feet beyond the teeth). In obstructed cases a rate of about 1 centimeter in 2 minutes (1 foot in an hour) is nearer the average. It is important that the tubes be marked at 6 inch intervals so that the patient or the nurse may be given a schedule to insure correct speed of swallowing, as a coil in the stomach from too rapid passage will sometimes check its advance.

RESULTS

Intubation for the relief of intestinal obstruction has been attempted on 16 individuals with failure in only 3. While the symptoms in one or two instances were mild, the patients as a rule, were desperately ill. In 9 instances function returned spontaneously following a variable period of decompression. Paralytic ileus and organic obstructions have responded in an essentially similar fashion (Figs. 1, 2, and 3). In the 4 cases in which the obstructing lesion was studied roentgenologically after the injection of a barium sulphate suspension through the tube, the point of closure was identified and the end of the tube was found to be lying within a finger's length of the obstruction itself (Fig. 4).

As the severity of intestinal obstruction can vary so widely, depending on the attendant circumstances, a brief sketch of each case follows. The data bearing upon the technique employed are presented separately in a summary table.

CASE REPORTS

Patients who became obstructed while under observation

Case 1. J.K., male, 73 years of age, with symptoms of chronic prostatism, became slowly obstructed by a carcinoma of the cecum. Intubation was carried out while he was in a state of shock from pain, distention, and vomiting. He was so relieved that he pulled the tube out later that night. At that time the abdomen was flat, peristalsis was normal, and his general condition was good. Subsequently, however, distention recurred and operation without intubation was attempted, but he died.

Case 2. W.S., male, 42 years of age, suffered a spontaneous rupture of a duodenal ulcer, was operated upon, and convalesced normally for 7 days. Fever and great abdominal distention, accompanied by streptococcic septicemia, then developed rapidly with a disappearance of peristalsis. The obstruction was of a paralytic type associated with infection. Intubation carried him over the period of ileus and ultimately, when he was able to eat, the tube was withdrawn without a recurrence of the symptoms.

Case 3. F.F., male, aged 68 years, had undergone an exploratory laparotomy because of sudden weight loss and constipation. His abdominal cavity was practically normal but the patient was in an agony of fear, believing that he was dying of cancer. His obstruction was of a paralytic type probably psychogenic in origin. A tube was passed and left in place until intestinal activity returned. When he was once more able to eat normally, the tube was withdrawn and he continued in good health, free from digestive complaint (Fig. 1).

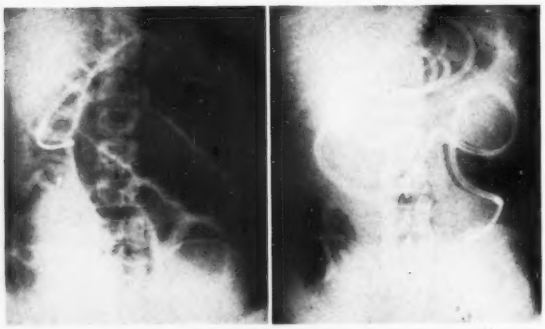


Fig. 2.

Fig. 2. Inflammatory intestinal obstruction. Case 4, K.A. a, left, Widely dilated small intestinal loops filled the abdomen. b, Decompression of the abdomen after intubation. At the time this film was taken the patient had swallowed the tube too rapidly with resultant coiling in the stomach.

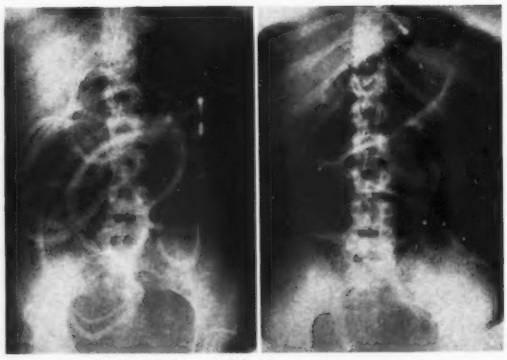


Fig. 3.

Fig. 3. Mechanical intestinal obstruction. Case 9, V.B. a, left, Marked small intestinal distention was present before intubation. b, Decompression of the abdomen following the passage of a No. 14 F. and a No. 3 F. tube.

CASE 4. K.A., male, aged 40 years, underwent a resection of gangrenous ileum which was found strangulated in a ventral hernia. Convalescence was interrupted by the occurrence of intestinal obstruction which came on with the development and drainage of a pelvic abscess and was probably based on inflammatory swelling of the intestinal wall. Following sustained decompression of the lower ileum he made an uneventful recovery (Fig. 2).

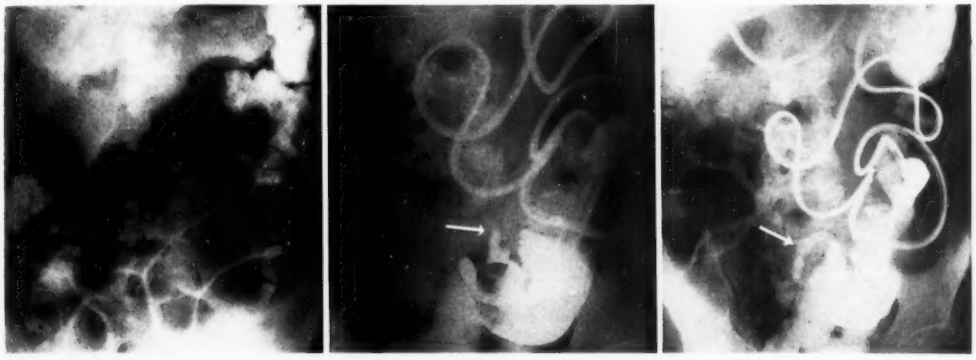
CASE 5. D.P., a young adult male, suffered slowly increasing intestinal obstruction from the sixth to the tenth day after an emergency operation for a gunshot wound of the abdomen which had punctured his stomach. The obstruction, which was long continued, was probably at the start on an inflammatory basis, with the mechanical factor of adhesions developing later. The point of obstruction was identified by the fluoroscopic observation of an opaque mixture injected through the tube. He was later operated on; the adhesions were released, and a satisfactory recovery followed.

CASE 6. J.M., male, aged 15 years, began to develop symptoms of intestinal obstruction 16 days after the surgical repair of a gunshot wound of the small intestines. The obstruction in this case was on an inflammatory basis. After adequate decompression of his lower small intestine, operation was rendered unnecessary by the patient's recovery.

CASE 7. G.L., a man of 62 years, became progressively distended with paralytic ileus during a 9 day period following the performance of a suprapubic cystotomy for the removal of a vesical calculus. Intubation was easily accomplished with relief of his symptoms and restitution of normal intestine activity. He remained free from digestive symptoms thereafter.

Patients admitted to the hospital because of existing intestinal obstruction

CASE 8. R.J., female of 27 years, had suffered three hospitalizations for intestinal obstruction following a cesarean section 4 years before. During one of these admissions she was operated on for lysis of adhesions. She was finally admitted after 4 days of vomiting with symptoms probably due to edema developing in the intestinal wall at a point of partial obstruction present since her former operation. The location of the obstruction was identified by fluoroscopy of an injected opaque medium. This attack was completely relieved by intestinal intubation



a. b. c.

Fig. 4. The localization of a mechanical obstruction. Case 12, W.S. a, Small intestinal distention was marked prior to intubation. The colon is outlined by the unexpelled residue of a barium enema. b, The small intestine has been decompressed by the passage of a No. 14 F. and a No. 3 F. tube. Barium has been injected down the tube and has regurgitated up a dilated loop of ileum. Its advance is blocked by a point of narrowing (arrow) just distal to the air-filled balloon and the tip of the tube. c, After film b was taken vigorous massage was successful in forcing barium through the constricted area of intestine (arrow) beyond which the opaque medium passed in a normal manner. Operation revealed a band of omentum binding this loop of ileum to the promontory of the sacrum.

Operation is contemplated as soon as she recovers from an acute pelvic inflammatory disease.

Case 9. V.B., a young negress, had suffered since the delivery of her child 2 months before from attacks of abdominal colic and vomiting, coming on with increasing frequency. Complete intestinal obstruction had occurred 48 hours prior to admission and was probably on a mechanical basis secondary to antecedent inflammation. The point of obstruction was located by the fluoroscopic observation of a suspension of barium sulphate injected through an intestinal tube and was found to be within 4 inches of the ileocecal valve. Normal intestinal activity eventually returned and she was discharged free from symptoms (Fig. 3).

Case 10. W.P., negro, male, 68 years of age, was admitted after 3 days of abdominal colic with vomiting and failure to pass gas or feces by rectum. Intestinal intubation relieved his symptoms. The obstruction was of mechanical origin due to a malignancy at the ileocecal valve. This lesion was likewise identified by the injection of a barium sulphate suspension. An ileocolostomy was performed and he has refused to have the mass resected.

Case 11. J.F., male, 31 years of age, was admitted with intestinal obstruction beginning 2 months after the drainage of an appendiceal abscess. Intubation brought complete relief. Subsequently an appendectomy was performed with normal convalescence. At operation a portion of the terminal ileum was found adherent to the abdominal wall. This was not released because of technical difficulties. He was admitted again with intestinal obstruction, swallowed the tube himself, and was relieved. This succession of relief, withdrawal of the tube and recurrence of symptoms occurred repeatedly for a month after which his digestive tract continued to function fairly normally. Obstruction in this instance was probably due to an underlying mechanical factor with superimposed local inflammation.

Patients with partial intestinal obstruction intubated primarily to locate the lesion after the failure of other diagnostic procedures

Case 12. W.S., the patient previously described as Case 2 was treated for septicemia by transfusion, sulphanilamide, the drainage of metastatic abscesses and supportive treatment until by the seventh week his temperature was normal and convalescence was established. Flatulence then returned, succeeded by slowly increasing distention, nausea, and colic. Roentgenoscopy showed gas filled small intestinal loops. The colon appeared normal when studied by barium enema. Constant suction drainage of the duodenum failed to relieve his symptoms. A tube was passed as far along the ileum as it would go, with prompt relief. A barium suspension was then injected locally and a point of partial obstruction was located. The abdomen was opened, a band of inflamed omentum was found constricting the ileum at the point indicated and with the release of this an uneventful recovery followed. (IV)

Case 13. R.O., female, aged 40 years, had suffered for 14 years from recurrent periumbilical pain with nausea and flatulence. Repeated gastro-intestinal roentgenological studies had failed to identify a diseased point but indicated abnormal small intestinal function. A tube was passed to the middle ileum beyond which point it would not go. A barium sulphate suspension injected through the tube demonstrated an acute angulation which next day was found, on surgical exploration, to have been pro-

SUMMARY OF 16 CASES OF INTESTINAL OBSTRUCTION TREATED BY SMALL INTESTINAL INTUBATION*

Subjects		Clinical state					Intubation procedures				Diagnostic value			Surgery
Groups	Patients	Duration of obstructive symptoms	Dehydrated	Distention	Colic	†Peristalsis	Vomiting	Fluoroscopic guidance	Time required to obtain relief	Time tube remained in place	Time suction maintained	Barium sulphate suspension injected	Point of obstruction found	Operative relief necessary
A. Patients becoming obstructed under observation	1 J.K.	7 ± days	Yes	++++	++	–	+	Yes	4 hrs.	9 hrs.	9 hrs.	No		Yes
	2 W.S.	5 days	No	++++	+++	– – –	++	Yes	3 hrs.	7 days	6 days	No		No
	3 F.F.	4 days	No	++++	+	o	+++	Yes	12 hrs.	5 days	4 days	No		No
	4 K.A.	17 days	No	++	++	++		No	4 hrs.	11 days	11 days	No		No
	5 D.P.	4 days	Yes	++++	++++	++++	+	No	6 hrs.	22 days	22 days	Yes	Yes	Yes
	6 J.M.	8 days	No	++	++	++	++	Yes	2 hrs.	2 days	2 days			No
	7 G.L.	9 days	Yes	++++	+	o	+			1 day	1 day			No
B. Patients obstructed on admission	1 R.J.	4 days	Yes	++	++++		++	No	24 hrs.	20 days		Yes	Yes	No
	2 V.B.	2 days	Yes	++++	++++		++++	Yes	6 hrs.	16 days		Yes	Yes	No
	3 W.P.	3 days		++	++		+	Yes	2 hrs.	12 days		Yes	Yes	Yes
	‡4 J.F.	3 hrs. to 4 days		o to ++++					1 hr. to 12 hrs.	1 to 10 days		No		No
C. Attempts made primarily to locate obstructions¶	1 W.S.	7 days	No	++	++++		+++	No	12 hrs.			No		No
	2 R.O.	14 years	No	o	++	++	o	Yes	6 hrs.	1 day	1 day	Yes	Yes	Yes
D. Failures	1 A.D.	1 day	Yes	o	o	o	+	Yes				No		
	2 W.B.	7 days	o	+++	++	–	++	Yes				No		
	3 L.V.	6 days	Yes	++	++	++	++	Yes				No		

*In every case gas was shown in the small intestine by roentgenogram and Wangensteen drainage had been tried without benefit.
†Peristalsis is recorded as normal, increased to ++++ or decreased to – – – – before becoming absent (o).
‡Several admissions.
¶See A-5, B-1, B-2, B-3.

duced by a ring of adhesions doubling back the ileum upon itself. Recovery was uneventful.

Failures

CASE 14. A.D., female, 75 years of age, was intubated 1 hour after operation for a strangulated femoral hernia. The procedure was attempted because inversion of a small gangrenous area of the intestinal wall had been necessary and ileus was expected. The tube could not be made to leave the stomach.

CASE 15. W.B., a laborer, 50 years of age, was intubated for progressive intestinal obstruction coming on insidiously weeks after an operation for the relief of a subdiaphragmatic abscess. He had suffered a spontaneous rupture of a duodenal ulcer a year and a half before, had developed a duodenobronchial fistula and at the time intubation was attempted was *in extremis* with ascites and an open external fistula. The tube could not be made to leave the stomach. Death ensued 48 hours later.

CASE 16. L.V., aged 81 years, was admitted with intestinal obstruction. A large diaphragmatic hernia was found and intubation was attempted. The tube could not be passed beyond the stomach. Death ensued and at necropsy it was found that the diaphragmatic hernia was inconsequential, the obstruction being caused by a Richter's hernia of the femoral canal.

It has been shown by Scheltema and by Einhorn that a tube left in the digestive tract will ultimately appear at the anus. Jones and Pierce have used a balloon on a tube and observed its passage throughout the gut, and the studies of Miller and Abbott have led to methods for rapidly reaching and emptying by double and triple lumen tubes any desired part of the small intestine. On the basis of their experience similar intubations have been accomplished in patients with varying types of obstruction of the intestine. From the diagnostic point of view, a study of the material aspirated is of importance, chemical analysis revealing the degree to which the electrolyte balance of the intestinal contents is disturbed and a microscopic examination of the sediment for blood or cells contributing evidence as to the nature of the obstructing lesion. A manometer or recording instrument connected with the balloon likewise is useful in estimating the motor responses of the intestine above the obstruction. The rapidity with which a distended and silent jejunum or ileum, or one vigorously manifesting reverse flow will revert to normal motor function when

decompressed has not previously been described. That such is the case and that it offers a valuable therapeutic method for the relief of such cases as are here reported is clear. We feel that the additional handling of a shocked patient, necessitated by the procedure, is justified by the benefit derived and that the delay caused in patients ultimately requiring surgery is not great enough to be of serious consequence. This delay can be lessened, moreover, by the use of the long tube from the start in a patient requiring decompression rather than by passing a duodenal tube first and attempting deflation of the jejunum and ileum only if the shorter instrument is inadequate. The tip of any tube is usually found to have entered the duodenum before it has been many hours in the stomach, so that if one has started with the long tube and the patient's response is not satisfactory he then need but inflate the balloon and allow the apparatus to advance as far as it will. The value of the procedure must depend on the judgment of the individual physician. When gangrene of the intestinal wall or a clear localization of obstruction, as in an external hernia, is present, small intestinal intubation constitutes a definite added hazard, but, excluding these cases, there still remain many for which small intestinal intubation should be tried before surgery, as a means of improving the patient's condition, of decreasing the technical difficulties of the operation, and not infrequently of rendering the operation unnecessary.

CONCLUSION

A double lumen tube or a pair of tubes may be passed rapidly down either a normal or an obstructed small intestine by inflating within the duodenum a rubber balloon on the end of the tube to a degree sufficient to stimulate propulsive peristalsis. This intestinal response takes place whether the obstruction is due to infection, mechanical occlusion, or paralytic ileus. Gas and fluid may be aspirated from the entire length of the small gut by the application of constant suction as the tube advances. Prompt and striking symptomatic relief occurs as the decompression of the intestine is accomplished.

By the injection of very small amounts of barium sulphate suspension down such a tube, by microscopic study of the intestinal contents aspirated, and by the character of the intestinal contractions, the location and often the nature of the obstructing lesion may be determined.

The advance of the tube has been found to proceed until the tip has reached the obstructed region.

In not a few instances decompression alone has released the obstruction, rendering operation unnecessary.

We wish to thank Dr. Eldridge L. Eliason and Dr. I. S. Ravdin for the privilege of reporting cases from their services and Dr. E. P. Pendergrass and his associates and Dr. C. Kenning and his associates for assistance with roentgenological phases of this work.

BIBLIOGRAPHY

1. Abbott, W. O., and Miller, T. G. Intubation studies of the human small intestine. III. A technique for the collection of pure intestinal secretion and for the study of intestinal absorption. J. Am. M. Ass., 1936, 106: 16–18.
2. Einhorn, M. An intestinal tube. New York M. J., 1919, 110: 456.
3. Jones, C. M., and Pierce, F. D. Mechanism and reference of pain from the lower intestinal tract. Tr. Ass. Am. Physicians, 1931, 46: 311.
4. Miller, T. G., and Abbott, W. O. Intestinal intubation: a practical technique. Am. J. M. Sc., 1934, 187: 595–600.
5. Scheltema, G. Permeation in the examination and treatment of the stomach and intestines. Arch. Roentg. Ray & Allied Phenomena, 1908–1909, 13: 144.
6. Wangensteen, O. H., and Paine, J. R. Treatment of acute intestinal obstruction by suction with a duodenal tube. J. Am. M. Ass., 1933, 101: 1532–1539.

MECHANICAL RESUSCITATION IN ADVANCED FORMS OF ASPHYXIA

A Clinical and Experimental Study in the Different Methods of Resuscitation

POL N. CORYLLOS, M.D., F.A.C.S., New York, New York

DEATH of the body as a whole, in higher organisms, said Paul Bert (1878), is always due to want of oxygen, whatever its cause may be. Life is continued so long as exchanges of oxygen and carbon dioxide in the tissues are carried on in a normal way. Gas exchanges depend upon and are regulated by their respective partial pressures and the aim of pulmonary ventilation is precisely to maintain these pressures at constant levels whatever may be the metabolic needs of the different tissues.

From the Departments of Surgical Research of Cornell University Medical College, and of Thoracic Surgery, of Metropolitan and Sea View Hospitals.

Fig. 1. Lung of dog 22. Use of the apparatus during 6 hours. Slight marginal consolidation of the left lower and partial consolidation of the left upper and right leaf of the accessory lobes.

On the other hand, the supply of oxygen and the removal of carbon dioxide are accomplished by the circulating blood. Therefore circulation is but a part of respiration and both co-operate in the closest way in order to maintain and preserve constant the conditions of life in the internal environment, the blood, as Claude Bernard said in his "Lessons on the Phenomena of Life."

Thus we arrive at the fundamental conception of the physiology of respiration—that respiration and circulation are so regulated as to keep both oxygen pressure and oxygen ion concentration very nearly constant in each part of the body, and that respiration and circulation are regulated by the changes in gas pressures in the tissues during life. "When once," says Haldane, "the fundamental fact is grasped that the flow of blood through the body is correlated with gas-pressures in the capillaries, the whole physiology of circulation appears in a new light. It is neither the heart nor the nervous centers which govern the circulation rate but the tensions of gas in the tissues as a whole; and they govern it with an accuracy and delicacy comparable to that with which they govern breathing. The heart and vasomotor system are only the executive agents which carry out the bidding of the tissues just as the lungs and nervous system do in the case of breathing."

Thus the problem of the regulation of circulation under normal conditions seems in the main to resolve itself into that of the "*regulation by the tissues of the amount of blood supplied to the heart*" (Haldane). In other words, it is the rate at which the systemic blood is allowed through the tissues from the

terminal arterioles and capillaries into the venous system that determines the amount of blood pumped by the heart. This rate, on the other hand, is determined by the amount of blood required to keep the diffusion pressures in them of oxygen and carbonic acid approximately constant. Y. Henderson has further developed this idea in his "venopressor reflex." Consequently the regulation of both circulation and breathing is essentially chemical and is governed by the same factors.

Thus it becomes obvious that any cause which interferes with the maintenance of normal partial gas pressures in the tissues may start asphyxia. Reduction of oxygen supply, —caused by obstruction of the air-ways or by decreased permeability to gases of the respiratory pulmonary membrane (inflammatory edema, destructive lesions) or by reduction of the respiratory field (retention of exudates, bronchial obstruction, atelectasis, pneumothorax, empyema), or by reduction of oxygen in the inspired air, has its immediate repercussion upon the function of the respiratory center. Anoxemia of the respiratory center causes increase of the respiratory rate which may or may not correct anoxemia. If it does not, a vicious cycle starts which, if not broken, leads to fatigue of the respiratory center and death. This cycle begins with tachypnea which washes out carbon dioxide and leads to apnea. Because of the elimination of the normal stimulus of the respiratory center there is a further increase in anoxemia; furthermore, because of the decreased partial tension of carbon dioxide, hemoglobin is saturated to a higher degree with the available oxygen (Bohr phenomenon). Thus cyanosis may be absent although anoxemia is increased because of the production of a more stable oxyhemoglobin compound under decreased carbon dioxide tension. On the other hand, the drop in partial pressure of carbon dioxide in the tissues decreases the muscular tonus necessary for the propulsion of the blood from the terminal arterioles and capillaries into the veins and the right heart (venopressor reflex of Y. Henderson). This author, to whom we owe so many important contributions on this subject, believes that the decrease of carbon dioxide abolishes muscular tonus. This is possible. However, as we do not know exactly what muscular tonus is, the actual existence of this reflex is subject to discussion. Keith called the terminal arterioles "peripheral hearts" meaning, as does Henderson, their importance in the propulsion of the blood. Whatever the mechanism may be, it is certain that a considerable decrease of carbon dioxide causes a drop of arterial pressure and peripheral stasis which further increases anoxemia.

Moreover, just as respiratory disturbances are caused by anoxemia so does impaired cardiac action due to organic diseases of the heart lead to anoxemia by defective circulation, blood stasis, and finally pulmonary edema. Thus, asphyxial death in cardiac disease is caused by the same mechanism as asphyxial death in pulmonary diseases or in obstruction of the air-ways.

These considerations were necessary, I believe, because, among many internists and surgeons, there is still a tendency, regarding the mechanism of asphyxia, to separate circulation from respiration and to disregard this close correlation and interdependence existing between them. Asphyxia can be defined as "the disturbance of gas exchanges in the tissues caused by abnormal breathing, or abnormal circulation, or of defective oxydative ability of the tissues"; therefore, it should be treated as a whole, with the main objective of re-establishing the normalcy of gas exchanges in the tissues.

It should always be borne in mind that progression of asphyxia due to defective oxygen supply may proceed with extreme rapidity. In fact, we possess no other reserve of oxygen in our organism than 600 cubic centimeters which is present in the 4,000 cubic centimeters of air contained in our lungs (which contains 15 per cent of oxygen). This amount is hardly sufficient for maintaining life for 2½ minutes when all supply from the outside is cut off. In fact, seven or eight breaths of a neutral gas, such as nitrogen, or hydrogen, bring loss of consciousness due to oxygen want and are followed by death if oxygen is not replenished.

The scope of this study does not allow a more detailed discussion of the chemical and

nervous regulation of respiration which I have presented elsewhere in their relation to the tuberculous lung (5, 6). I shall mention here only two more points. First is the so called Herring-Breuer reflex in which expansion of the alveoli causes arrest of inspiration and starts expiration, and collapse of the alveoli causes arrest of expiration and starts inspiration. The legs of these reflexes are represented by afferent and efferent fibers included in the vagus acting upon the respiratory center. Conversely, through this reflex, distention and collapse of the lung in the mechanical treatment of asphyxia may act as powerful stimuli upon the respiratory center. The second point to be mentioned is the significance of rhythmic respiratory variations of intrapulmonary and intrapleural pressures upon the function of the heart. It is obvious that marked increase of the intrapulmonary and, consequently, of the intrapleural pressures hinder the suction of blood into the large veins and interfere with their emptying into the right heart. In these cases venous blood pressures rise and the amount of blood passing into the right heart, the lungs, and back into the left heart, may be considerably decreased. However, as will be shown later, this phenomenon is of no great importance so long as intrapulmonary hyperpressures are not very high or of long duration; this is due to the marked differences of blood pressures in the large arteries and the large veins.

ASPHYXIA

Causes. The causes producing asphyxia may be divided into seven major groups (Meakins and Davies).

1. Insufficient partial pressure of oxygen in the inspired air (high altitudes).
2. Obstruction of air passages or resistance to respiration.
3. Obstruction to the passage of gases from the alveoli to the blood (edema, inflammation, exudation, destructive lesions, emphysema).
4. Alteration of oxygen carrying capacity of the blood (anemia; carbon monoxide, nitrate, or chlorate poisoning).
5. Circulatory failure.
6. Pollution of the oxygenated blood by its mixing with the venous blood. (Uneven ventilation of the lungs, unaerated channels, congenital cardiopathies, and the like.)
7. Inhibition of oxydative processes in the tissues (cyanide poisoning).

Of all forms of asphyxia the most important for the internist and the thoracic surgeon are the ones due to obstruction and resistance to respiration, to inflammatory edema of the alveolar membrane, to the creation of unaerated channels with pollution of the oxygenated blood, and to the toxic action upon the respiratory center of anesthetic gases.

Forms of asphyxia. Asphyxia should be divided, according to its degree into three forms.

1. Slight asphyxia. This form is characterized by persistence of respiration and circulation; dyspnea is present and is accompanied by a variable degree of cyanosis. The degree of cyanosis, however, is not always proportionate to the degree of asphyxia. Slight resistance to respiration by partial tracheal obstruction may cause considerable cyanosis with gasping for air, because of retention of carbon dioxide, although the grade of anoxemia may be slight. On the contrary, in the presence of extensive involvement of the bronchial and alveolar mucosa, cyanosis may be slight or absent (gray cyanosis) while periodic or shallow rapid breathing indicate marked anoxemia. Gray cyanosis follows considerable washing out of carbon dioxide (Bohr phenomenon), and shows an advanced degree of anoxemia.

2. Moderate asphyxia. If not corrected in time, slight asphyxia progresses rapidly to a more advanced stage. The rate of respiration becomes greatly increased: periodic and shallow breathing develops, leading to fatigue of the respiratory center; arterial blood pressure falls after a temporary elevation; venous pressure rises, and convulsions may appear at this phase.

3. Severe asphyxia. These forms are characterized by apnea, extreme drop of arterial pressures and failing or arrest of the heart. After convulsive attacks the body gradually relaxes and becomes flaccid. Consciousness is gone, the eyes are glassy, corneal reflexes disappear, and pupils begin to dilate. The

lower jaw relaxes because of gradual suppression of muscular tonus. Spurious inspiratory movements of lips and nostrils replace real respiratory ones and no effective respiratory movements can be detected. The skin is clammy and covered with cold sweat. The radial and femoral pulses are no longer perceptible. Patella reflexes disappear and the sphincters relax. Heart beats are uncertain and it is impossible to say at this phase whether the patient is still alive or that death has occurred.

These are the three principle forms of asphyxia with which we are usually faced. All intermediate forms may be encountered and the passage from one to the other may occur with disconcerting speed.

Time is of paramount importance in the management of asphyxia. One should never forget that it is easy to cope with slight asphyxia whereas it is very difficult, if not impossible, to resuscitate a man or animal after the heart has ceased to beat. Therefore, at the slightest threat of asphyxia, measures for resuscitation should start at once without waiting for possible spontaneous resumption of respiration.

The considerations mentioned give the key to the alarming rapidity with which asphyxial death may occur in patients with pulmonary diseases. In fact these patients are strongly handicapped to any increase of their anoxemia because of their chronic anoxemia due to the pulmonary disease. This factor is of paramount importance in the complete understanding of asphyxial accidents in these patients and of the requirements for successful resuscitation. Therefore, chronic anoxemia deserves special consideration.

Chronic anoxemia. In cases with chronic pulmonary suppuration, such as tuberculosis, abscess of the lung, bronchiectasis, extensive silicosis or malignancies and more so in acute pulmonary diseases especially in bronchopneumonia, anoxemia is always present because of uneven pulmonary ventilation, inflammatory edema of the respiratory membrane, partial destruction of the pulmonary parenchyma or atelectatic and fibrotic disablement of a portion of the lung. As a rule compensatory polycythemia is present in these cases. The slightest increase of anoxemia in these patients may be the cause of asphyxia and rapid death, apparently disproportionate to the cause which has produced it. Thus in advanced pulmonary tuberculosis even moderate pulmonary hemorrhage, or passage into the bronchial tree of a few cubic centimeters of pus from an empyema cavity, or obstruction of a bronchus of the healthy lung with bronchial exudate coming from the diseased side, or spontaneous pneumothorax of the diseased or of the contralateral side, may cause rapidly lethal asphyxia. For example, a patient who during bedrest is only slightly dyspneic, and who, disobeying orders, gets out of bed to go to the lavatory, may drop dead because of this otherwise slight exertion.

The knowledge of this chronic anoxemia, to which the organism may be temporarily adjusted by decreased oxygenation rate in the tissues and possibly by active oxygen secretion of the alveolar epithelium (Ludwig, Haldane), is of the greatest importance to the internist and the thoracic surgeon. Haldane wrote in his classic *Treatise on Respiration:* "If there were only one clinical lesson derived from the perusal of this book I hope that it would be that chronic anoxemia is a very serious condition the continuance of which ought to be prevented if at all possible."

These considerations make it easy to understand the dangers to which these patients are exposed when they are operated upon. It is my contention that the prohibitive mortality at the beginning of thoracic surgery, more especially in tuberculosis of the lung and other chronic suppurations of this organ, was due to the imperfect knowledge of chronic oxygen want. Respiratory failures, acute dilation of the right heart, and cardiac decompensation were the usual diagnoses on the death certificates. We know today that all these vague terms must be replaced by "anoxemia." If actually, without any radical changes in operative technique, we are able to operate upon patients with even far advanced and bilateral pulmonary tuberculosis or bronchiectasis with a remarkable degree of safety, it is because of better knowledge of chronic anoxemia, of improved administration

of anesthesia, and of more rational pre-operative preparation and postoperative management of these patients. This has been accomplished by a closer correlation between operating work and the research laboratory. Chest operations are conducted today with the accuracy and minute precautions of physiological experiments; conversely laboratory animals are subjected to similar operations after previous preparation rendering their condition as similar as possible to our patients (5).

The result of this close co-operation of operating room and laboratory during the last 5 years in the two departments of thoracic surgery under my direction, in the Metropolitan and Sea View Hospitals of the City of New York, has been that the mortality has fallen from 20 per cent of 5 years ago to below 8 per cent even though patients with far more advanced conditions are being submitted to surgical treatment, especially during the last 3 years.

The ideas on asphyxia and resuscitation expressed in this study have been developed during this work. They may, occasionally, be in disagreement with generally accepted opinions; nevertheless they are backed, I believe, by substantial clinical and experimental evidence.

MANAGEMENT OF ASPHYXIA

Little will be said regarding the first two forms of asphyxia. Careful removal of any foreign material obstructing the bronchi followed by manual rhythmic compression of the chest and inhalation with 7 to 10 per cent carbon dioxide in oxygen is generally sufficient to restore regular respiration. However, prolonged administration of carbon dioxide in oxygen (5 to 7 per cent) may be required after resuscitation until the danger is over. This is especially important in carbon monoxide poisoning in which protracted oxygen-carbon dioxide inhalation treatment is of paramount importance for complete recovery and prevention of complications.

More important and far more difficult is the management of the severe forms of asphyxia. I want to insist upon the point that in cases with apnea no time should be lost with attempts of resuscitation by inhalation and manual artificial respiration. This applies not only in chest surgery where manual resuscitation is out of the question but also in all cases of asphyxia in which the patient does not breathe. It is obvious that in such cases oxygen has to be forcibly introduced into his lungs. Even beginning flaccidity causes the chest to collapse in position of extreme expiration, so that little air, if any, can be aspirated into the lung by the expansion of the chest following the compression by the methods of Shaeffer or Sylvester or any other. I agree perfectly with Yandel Henderson that "the inspirations that occur between compressions (in manual artificial respiration) are produced wholly by the tonic elasticity of the victims' mid-expansion. After the body is flaccid no form of manipulation can induce the slightest inspiration."

Mouth-to-mouth insufflation. The mode of resuscitation that has given me the best results in cases of severe asphyxia, is the immediate application of mouth-to-mouth insufflation. I know of no method of resuscitation more efficient and more rapidly effective. In a number of instances with patients apparently dead, this method has produced striking resuscitations. It is a puzzle to me that this mode of resuscitation is not mentioned in the treatise of Haldane or in the writings of Yandel Henderson on resuscitation. Waters and Bennet, on the contrary, in a recent paper in which they had studied the respective merits of different methods of manual resuscitation concede that the best of them (Sylvester's) is "second only to mouth-to-mouth insufflation." Physiologically this is a sound procedure because it allows the immediate administration of the correct mixture of carbon dioxide in oxygen, under the correct conditions of temperature, moisture, pressure, and at the proper intervals. Moreover, it takes advantage of the powerful Herring-Breuer reflex.

Such striking results have been obtained by this procedure that it has been routinely used in my services, during the last 10 years in all patients with asphyxia. Patients have been revived in whom the heart beats could hardly be detected and only by the movements of intracardiac needle, and in whom

there was loss of muscular tonus with dropped jaw, dilated pupils and abolished glottis reflex.

This method, however, presents two serious drawbacks. One, common to all resuscitation procedures, is that the air-ways are not always patent. In the operating room or in the postoperative wards this is easily insured by the introduction of an intratracheal catheter. In the field this can be also easily accomplished with Flagg's suction bottle and the introduction of a pharyngeal air-way or of a Magill catheter. The second drawback, specific to this procedure, is the exposure of the operator to contamination by tuberculous patients, and the impossibility, because of the fetor, of carrying the insufflation for any length of time in cases with anaerobic suppuration of the lung.

It was precisely the necessity of replacing the surgeon or the anesthetist by some mechanical device accomplishing the same or similar work that has induced me to investigate the different apparatus on the market based on the pulmotor principle. Thus I was led to the experimental and clinical study of the apparatus known as the E & J resuscitator.

Mechanical resuscitation. The E & J apparatus consists of two parts. One acts as a simple inhalator. The other as resuscitator. The latter is a mechanical device composed of a number of valves which are activated by the pressure of the usual oxygen or carbon dioxide in oxygen mixture delivered in tanks under a pressure of 2,000 pounds. When a positive pressure of 14 millimeters of mercury is built up in the mask of this apparatus the valves are automatically reversed and a suction of −9 millimeters of mercury is produced which is again followed by a positive pressure of 14 millimeters of mercury, and so on. In other words, it is a machine based on the principle of the automatic type of the Draeger pulmotor, in which the pressures are constant whereas the volumes of gas vary with the capacity of the lung of the patient.

Such an apparatus, however, was subject to a number of serious criticisms which required thorough experimental study before any clinical trial could be attempted. The principal objection is that intrapulmonary

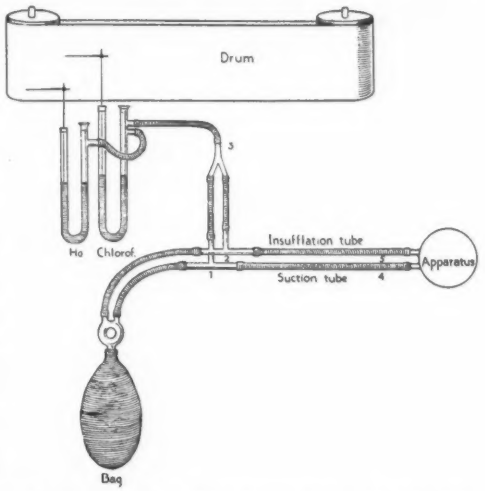


Fig. 2. Testing the E and J resuscitator. The two tubes coming from the apparatus, *4* and *5*, are connected with two T tubes, *1* and *2*. The vertical branches of these tubes are connected with a Y tube, *3*, which is connected with two registering manometers, mercury and chloroform. On the other hand the two tubes, *4* and *5*, are connected with a rubber bag representing the lung.

and intrapleural pressures produced by this apparatus during inspiration and expiration, are positive during inspiration and negative during expiration, that is the opposite to those in normal respiration. Therefore, a list of requirements was drawn which was submitted to strict experimental investigation. These requirements are the following:

1. Is this apparatus technically reliable and constant in its action? Is it constant in both positive and negative pressures independently of pressure in gas tank; does it function regularly under prolonged action?

2. Is its prolonged use without any danger, either organic upon the lung or functional upon respiration and circulation?

3. What is the efficacy of this apparatus in cases of asphyxia; mechanical (submersion, laryngeal, or tracheal obstruction) or chemical (anesthetic gases)?

4. Can this apparatus be used, experimentally, in long operations upon intrathoracic organs (heart, lung, and esophagus) in which the pleural cavity is maintained open for a long period (over 3 hours)?

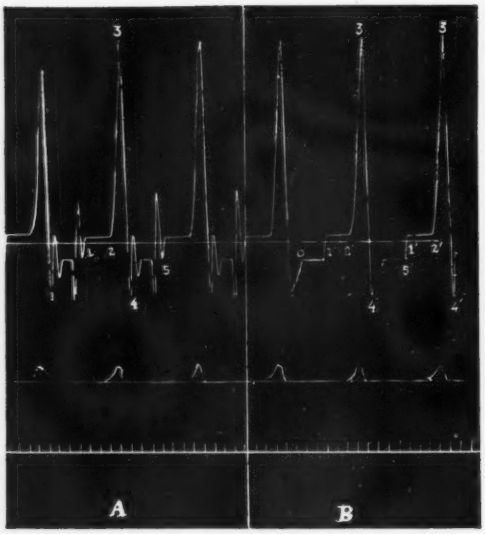


Fig. 3. Graphs taken with the outlay shown in Figure 2. A, shown above, the actual graphs of the chloroform manometer and, below, of the mercury manometer. Times are registered in seconds. *1*, *2* and *3* show the building up of positive pressure (14 mm. Hg.), *4* and *5* the negative pressure. B shows the same graph when the parts of the curve representing opening and closing of the valves had been eliminated in order to show more clearly the function of the apparatus.

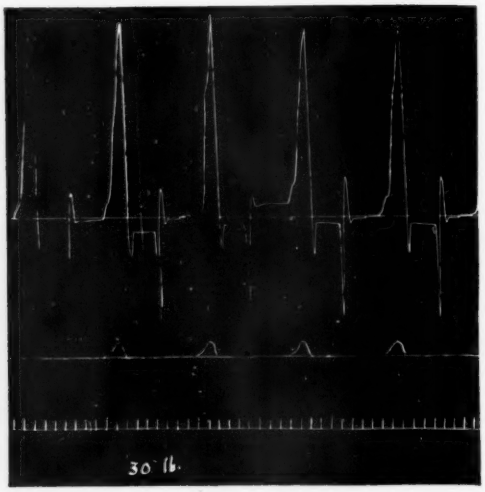


Fig. 4. Tracing taken while the tank was almost empty and pressure in it was of 30 pounds only (initial pressure 2,000 pounds). A comparison of this graph with Figure 3 shows no changes in the shape of the curve.

5. What are the results, if any, obtained from asphyxiated and apneic animals, the lungs of which have been maintained ventilated by this apparatus, when direct massage of the heart is applied several minutes after complete arrest of cardiac action?

6. What is the action of this apparatus on humans who have developed apnea in the course of, or following, thoracic operations?

EXPERIMENTAL INVESTIGATION

It is obvious that the points raised above could not be answered satisfactorily by superficial inquiry or with preconceived ideas for or against the principle upon which this apparatus is based: Therefore these problems were submitted to a long experimental investigation which was carried out in the laboratory of Surgical Research of Cornell Medical College, with the collaboration of Dr. G. L. Birnbaum. Forty-two dogs were used. A number of clinical observations and experimental results gathered during previous experimental and clinical work on submersion (to appear shortly) have been used in this investigation.

1. *Mechanical efficiency of the apparatus.* The function of the apparatus was first checked by graphs taken with mercury and chloroform manometers. For this purpose the mask of the apparatus was connected with a rubber bag representing the lung (Fig. 2). In the two tubes leading from the apparatus to the mask were interposed two T tubes, *1*, *2*, the vertical branches of which were connected with a Y tube, *3*, which was connected with two manometers, one chloroform and the other mercury. Thus the tubes of the apparatus, *4*, *5*, were connected with the bag and the manometers.

The study of the graphs taken with this arrangement (Fig. 3) showed that the up and down strokes, representing positive (upward) and negative pressures, were perfectly regular; their heights above and below the basal line were equal and their spacing the same.

The graph of Figure 3, gives a clear idea of the functioning of the apparatus. At the start the pressure is slightly positive for a short while, *1* to *2* (Fig. 3A); then it rises

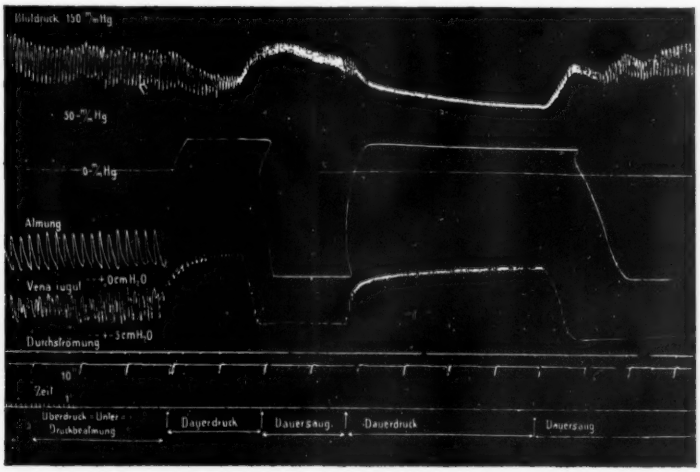


Fig. 5. Action of intrapulmonary hyperpressure (20 cm. of water) and hypopressure (−20 cm. of water) upon arterial and venous pressures. From up down, arterial pressure, intrapulmonary pressure, venous pressure and time in seconds. As the intrapulmonary pressure rises the arterial pressure drops and venous pressure rises (graph of Rost).

rapidly to 14 millimeters of mercury, *3*, and falls almost vertically to minus 9 millimeters of mercury, *4*, from which it rises to a slightly negative pressure, *5*. If we neglect the intermediate oscillations due to the play of the valves and the "jumps" of the manometer (Fig. 3B) we can distinguish in the action of the apparatus two phases: (1) *1′*, *2′*, *3′* of insufflation and a second, *3′*, *4′*, *5′*, of suction. Before the rise as before the fall, we find a period of slightly positive, *1–2* and another of slightly negative, *o–1′* pressures which constitute two-thirds of the cycle.

As the tempo of the cycle depends upon and is regulated by the pressure obtained, it becomes more rapid when the capacity of the lung (the bag here) is decreased and slower when the capacity is increased. Likewise it is influenced by the "volume" of gas allowed to enter the apparatus. Thus, obstruction of the air passages is immediately signaled by the rapid tempo of the apparatus.

On the contrary, the changes occurring in the pressure in the gas tank as it empties were shown to be without any marked influence upon the pressures and rhythm of the respiratory cycle. Tracings were taken with pressures in the tank decreasing from 1800 to 30 pounds. Figure 4 shows that there were no appreciable changes either in the height or in the frequency of the oscillation when the pressure of the tank has fallen to only 30 pounds.

The apparatus was tried in continuous function for 12 hours without showing any changes in the tracings.

It was concluded, therefore, that the mechanical construction of this apparatus insures a regular, accurate, and prolonged function which is maintained unchanged until the tank is practically empty (30 pounds' pressure).

Effects of prolonged action of the apparatus upon normal dogs (without previous operation). The problem to solve was whether prolonged use of the apparatus on normal dogs caused any organic lesion of the lung or any functional disturbances of respiration and circulation, and for how long the use of this apparatus could be prolonged without any untoward effects.

Before giving our experimental findings I think it is of interest to quote from the literature on the effects on intrapulmonary hyperpressures and hypopressures.

Chillingworth and Hopkins (1930) carried

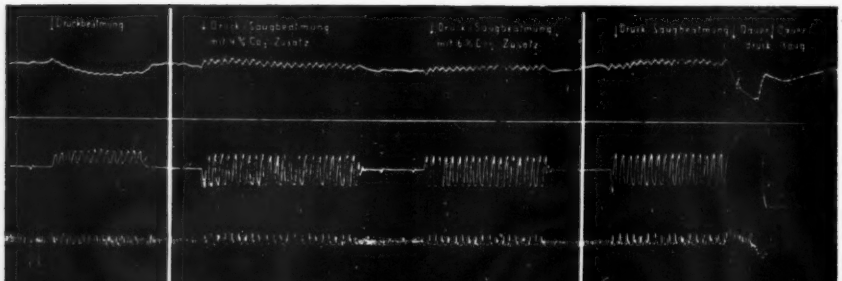


Fig. 6. Same experiment as in Figure 5 showing that the effects of intrapulmonary hyperpressure and hypopressure upon arterial and venous blood pressure are much less marked when instead of pure oxygen a mixture of oxygen carbon dioxide was used.

out experimental work on dogs in order to test whether positive intrapulmonary pressures were likely to cause abnormal resistance to circulation and heart failure. They found that when the lung was inflated with air under pressure to or above 80 millimeters of mercury and this pressure was sustained for 10 seconds, there was considerable fall of the systemic arterial pressure while the venous pressure increased. In one experiment, in which the intrapulmonary pressure was brought to 80 millimeters of mercury the arterial pressure fell from 156 millimeters of mercury to 26 millimeters of mercury and the venous pressure rose to 120 centimeters of water. On releasing the intrapulmonary pressure the arterial pressure gradually returned to 128 millimeters of mercury, reaching this level within one minute. Haldane commenting on these findings says: "It is obvious that high intrapulmonary pressure could not cause heart failure in consequence of an abnormal strain thrown on the right ventricle owing to excessive resistance to the outflow of blood from it, because there was little or no blood entering the ventricle to be pumped outward."

A thorough experimental work was carried out by Rost (1932) on the effects of intrapulmonary hyperpressure and hypopressure in dogs. In Figure 5, representing a graph of this author, are registered the results of hyperpressure (20 centimeters of water) and hypopressure (−20 centimeters of water) on a dog anesthetized with chloral and curarized. In this graph are recorded, from up down, arterial pressure (femoral artery), intrapulmonary pressures (tracheal cannula), venous pressure (jugular vein), venous blood flow and time in seconds. It is clearly shown in this graph that as the intrapulmonary pressure is raised venous pressure rises and arterial pressure falls. The fall of the former being proportionate to the duration of the intrapulmonary hyperpressure. When the intrapulmonary pressure was decreased to −20 millimeters of water the arterial rose and the venous pressure dropped. The second period of hyperpressure in this curve was prolonged for 60 seconds. The arterial pressure showed a much greater drop; even then, however, immediately after release of the intrapulmonary pressure both arterial and venous pressures were restored to normal. Continuation of this experiment for over an hour did not produce any damage to the lung or to the circulation nor was the flow of the venous blood influenced. It is of importance to note that

when instead of plain oxygen, this author used 4 and 6 per cent of carbon dioxide in oxygen mixtures all other conditions of the experiment being the same, the changes in venous and arterial pressures were much less marked. Figure 6, represents the results obtained by using, respectively: pure oxygen (right end of the curve), and 4 and 6 per cent mixture of carbon dioxide in oxygen (middle part of the curve *b* and *c*). The fall of arterial and the rise of venous pressures during hyperpressures, sharply marked when the dog was breathing pure oxygen, *a*, are hardly noticeable or absent when carbon dioxide in oxygen mixture was given, *b*, *c*, In all these experiments the dog was curarized and anesthetized with chloral.

Rost reports that animals anesthetized with ether or chloral did not present any untoward after-effects following prolonged application of hyperpressure or hypopressure. Application of the same technique on the human did not show any untoward effects. Electrocardiograms taken at the end of the experiment showed no changes.

In our experimental study 7 dogs, of 10 kilograms average weight, were submitted to the action of the apparatus. They were all anesthetized by sodium amytal (55 milligrams per kilogram intraperitoneally, 10 per cent solution) or with ether. The duration of the experiments varied from 1 to 8 hours without interruption. No intratracheal cannula or air-way was used.

When the action of the apparatus did not last over 1 hour and 30 minutes, there was no period of apnea when the mask was disconnected, and the animal immediately resumed normal breathing. On the contrary, when the action of the apparatus was prolonged for 6 hours and over, there was often a period of apnea. In one animal (dog 22, 7 hour experiment) apnea lasted 4 minutes and 11 seconds. In another animal (dog 23, 6 hour experiment) apnea lasted 1 minute and 40 seconds. In both, normal respiration resumed spontaneously and proceeded normally.

In dogs 26, 27, and 28, on the contrary, with duration of the experiment of, respectively, 3 hours and 20 minutes, 6 hours, and 4 hours, there was not the slightest apnea. In

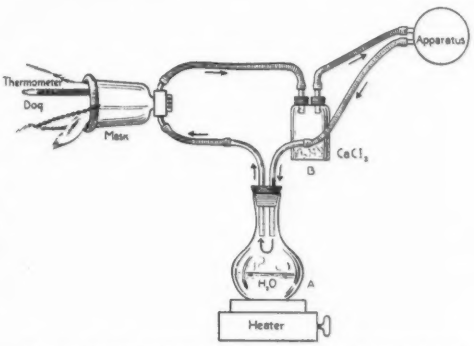


Fig. 7. Heating of gases going from E & J apparatus to the dog (Exp. 28).

dog 24 the apparatus was connected with a tank of compressed air; in the others with a tank of 5 per cent carbon dioxide in oxygen mixture.

However, an important complication developed in the course of this investigation. Dogs 22, 23, 24, and 25 died between 12 hours and 5 days after the experiment although blood pressure and pulse rate had come back to normal. At the autopsy relatively slight pulmonary or other lesions were found, which could not explain death. Figure 1 shows the lung of the most affected of these animals (dog 22). Suspecting chilling as a possible cause of these deaths because the rectal temperature in all these dogs had dropped to around 31 degrees C. at the end of the experiment, we endeavored to avoid loss of heat and to maintain the body temperature around 38 degrees C. rectally. Dogs 25, 27, and 28, in which such precautions were taken, did not show the slightest trouble following the experiment. Dog 25 especially in which a heating and humidifying device of the gas mixture was used (Fig. 7.) showed the most uneventful recovery.

I deem it of interest to give here a short résumé of the protocols of these animals.

Experiment 22. Male dog, 12½ kilograms. The action of the resuscitator was prolonged for 6 hours. Carbon dioxide in oxygen, 5 per cent was used. When the resuscitator was disconnected the animal presented apnea which lasted 4 minutes and 11 seconds. Respiration continued normal thereafter. However, the animal was deeply in shock, with corneal and light reflexes absent. This animal was

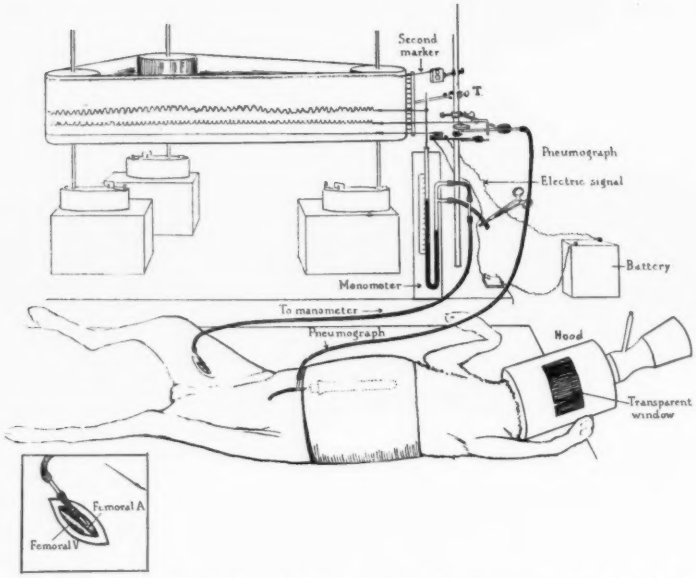


Fig. 8. Technique of experimental study in asphyxia submersion. The head of the dog, previously anesthetized, was introduced into a metallic cylinder, the hood. One base of this cylinder was closed by a rubber membrane perforated in its center. To the other base of the cylinder was soldered a funnel-like device through which water could be poured into the hood. The neck of the animal was shaved and anointed with petrolatum. The hole in the rubber membrane was slightly stretched and the head of the animal passed through it. Thus the base of the hood was closed watertight and the head of the animal could be submerged by filling the hood with water. No undue stricture was exerted upon the neck of the animal. A pneumograph was applied on the chest of the animal and a cannula was introduced into the femoral artery. This technique allowed continuous recording of respiratory movements and blood pressure.

found dead the next morning, about 10 to 12 hours after the experiment. Autopsy showed slight consolidation in the left lower and partial consolidation of the left upper lobe and right leaf of the accessory lobes, as shown in the photograph of the specimen (Fig. 1.).

It was thought that the animal probably died from oxygen pneumonia, since he was breathing in an atmosphere of 95 per cent oxygen and in this instance the partial tension of oxygen in the mixture was 722 millimeters of mercury instead of 149 millimeters of mercury, as in atmospheric air.

Histological section showed: pulmonary congestion with moderate edema in the areas of consolidation.

However, the rectal temperature of this animal at the end of this experiment was 31 degrees C. instead of 39 degrees C. which is normal for the dog. This subnormal temperature was attributed to the rapid evaporation taking place in the lung, to the low temperature of the gases, and the immobility of the anesthetized animal. Moreover, since the gases were dry, they might have caused pulmonary irritation by their dehydrating effect.

For the solution of this problem the following experiments were carried out:

Oxygen-carbon dioxide mixture was replaced by plain compressed air in order to confirm or rule out oxygen pneumonia.

Experiment 23. Male dog, 10½ kilograms. Sodium amytal was given intraperitoneally, 55 milligrams per kilogram. The apparatus was connected with a tank of compressed air.

This experiment was carried out for 6 hours, all other conditions being the same as for experiment 22. The animal's temperature at the end of the experiment was, again, 31 degrees C. The animal presented apnea when the resuscitator was disconnected; its duration was 1 minute and 40 seconds. This animal died 11 hours after the experiment.

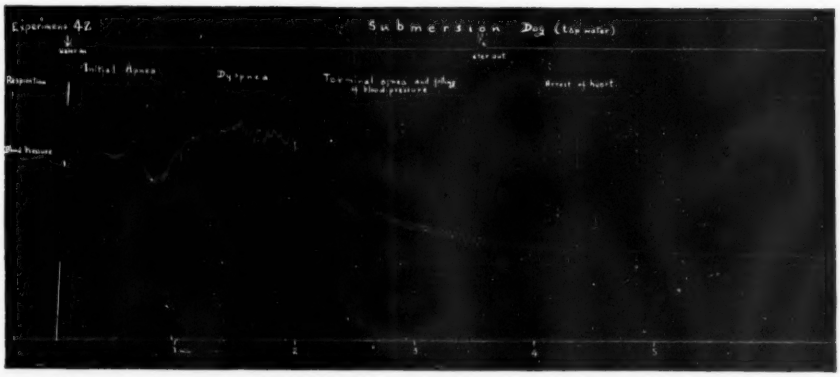


Fig. 9. Graph of submersion in water (dog, technique of Fig. 8) showing the four phases of asphyxia in submersion. Upper curve, respiration; lower, blood pressure. W, Water was poured into the hood. It is followed by reflex arrest of respiration (initial apnea) and elevation of blood pressure. *1–2*, first phase, duration 1 minute. *2 – 3*, Respiration becomes irregular and blood pressure continues to rise— second phase, of dyspnea, duration 1 minute. From *3 – 4* respiration gradually stops and blood pressure drops rapidly—third phase of terminal apnea, duration 1 minute. *4 – 5*, Drop of blood pressure continuous and at the end the heart stops—fourth phase of arrest of the heart.

Autopsy showed again slight marginal consolidation which could not be the cause determining death.

Thus the cause of death in the previous experiment (dog 22) was not necessarily oxygen pneumonia.

The above findings were further verified by two additional experiments:

Experiment 24. The action of the apparatus was prolonged for 1 hour, using carbon dioxide in oxygen (95–5 per cent). Dog, 9½ kilograms; anesthesia with amytal 50 milligrams per kilogram. The rate of the apparatus was 15 per minute. Gas pressure in tank was 1700 pounds. Other conditions were the same as in experiments 22 and 23. The rectal temperature at the end of the experiment was 32 degrees C. These animals presented no apnea. Ocular and corneal reflexes were normal, anus only slightly patent. The last day of life the dog appeared rather sick. He died 5 days later. Postmortem examination revealed no appreciable pulmonary lesions.

Experiment 25. Dog, 9 kilograms. Sodium amytal anesthesia, 50 milligrams per kilogram body weight. The apparatus was connected with a tank of carbon dioxide in oxygen (95–5 per cent); initial pressure in tank was 1800 pounds. This experiment lasted 3½ hours. Again, at the end of the experiment the temperature had dropped to 31 degrees C. The animal died within 10 hours. At autopsy no sizable lesions of the lung were found.

These experiments suggested that the cause of death might have been related to an excessive chilling of the animals. It was therefore interesting to prevent chilling, eliminate drop of temperature, and see whether death could be prevented, all other conditions remaining the same.

Three experiments were carried out:

Experiment 26. Dog, 18 pounds. Amytal, 55 milligrams per kilogram of body weight. This experiment was conducted exactly as experiments 22, 23, 24, and 25, the only differences being that measures were taken to prevent a drop of temperature by covering the animal with several blankets between which an electrically heated pad was placed. Rectal temperature was maintained constant between 38.5 and 39 degrees C. (readings taken every 5 minutes). Rate of the resuscitator was 20 per minute. Initial pressure in the tank was 1300 pounds. Carbon dioxide in oxygen mixture 5 per cent. Action of the apparatus was prolonged for 3 hours and 20 minutes. At the end of the experiment there was no apnea. Corneal reflex was active. Reflexes to light normal; anus contracted. Animal was out of anesthesia 2 hours after the end of the experiment, up on his feet, and he ate and drank. This dog remained in perfect condition.

Experiment 27. Apparatus was connected with a tank of compressed air as in experiment 23. Duration of experiment 6 hours. Dog, 8 kilograms; anesthesia with sodium amytal, 55 milligrams per kilogram body weight. Rate of apparatus 18 per minute. This rate was obtained by turning down clockwise the regulating valve of the apparatus so that the gases were turned off more than half. The animal's own respiration rate before the mask was applied was 14 per minute. Rectal temperature was main-

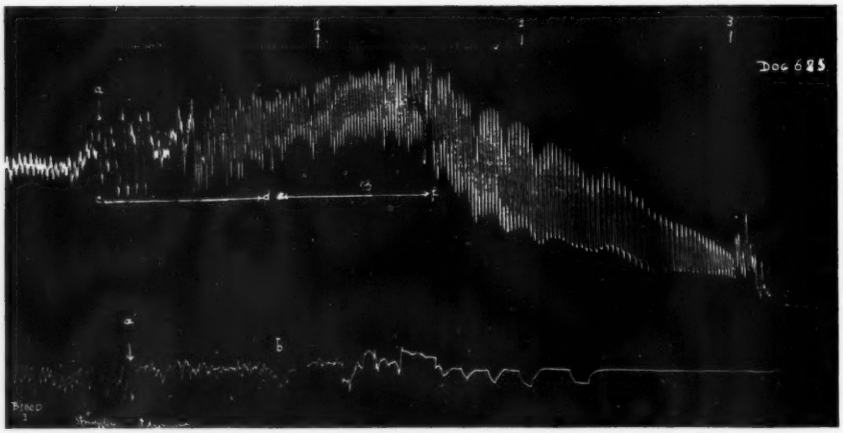


Fig. 10. Similar experiment as in Figure 9. As in that graph the four phases are clearly shown.

tained at 38.5 degrees C. Pressure in the tank at the start of the experiment was 2000 pounds; at the end of the experiment it was 450 pounds. No apnea occurred and the animal was up and about 3 hours after the end of the experiment. He remained in perfect condition.

The above experiments (26 and 27) have shown conclusively that the death of dogs 22, 23, 24, and 25 was not due to oxygen pneumonia and the hypothesis of death caused by excessive chilling was corroborated. In fact, when the loss of heat was prevented the dogs were able to stand 6 hours of continuous action of the resuscitator, using a 95–5 per cent carbon dioxide in oxygen mixture or compressed air without any evil after-effect.

This question of death due to the lowering of the temperature of the animal was of particular interest. Therefore, in order to eliminate any possible error, in the following experiment (dog 28) the gases were heated and humidified before being led into the mask, by passing through a two-tubed bottle containing water heated to about 100 degrees C. (Fig. 7). The animal was not covered with blankets and electric pad. The protocol of this experiment follows.

Experiment 28. Male dog, weight 25 pounds. Sodium amytal was given intraperitoneally, 55 milligrams per kilogram body weight. Apparatus connected with carbon dioxide in oxygen (95–5 per cent). Layout of experiment as in drawing (Fig. 7). A large bottle containing water which could be heated was interposed in the insufflation tube of the E & J resuscitator and a similar bottle containing calcium chloride was interposed in the suction tube going from the mask to the machine. Thus the gases going to the mask were heated and humidified while the moisture in the gases coming from the mask was intercepted in bottle *B* in order to avoid possible damage to the apparatus. The temperature of the gases in the mask was checked by a thermometer slipped under the mask; the temperature of the body was recorded by another thermometer in the rectum. The duration of this experiment was exactly 4 hours; 2½ cubic centimeters more of 10 per cent solution of amytal was given during this time to maintain the animal under anesthesia. The temperature in the mask varied from 37 to 39 degrees C. and was regulated by turning the heater on or off. Rectal temperature stayed 38 degrees C. throughout the experiment. Pressure in the gas tank was 1500 pounds at the start and 100 pounds at the end of the experiment. The rate of the apparatus was 12 at the beginning, 14 in the middle of the experiment, and 24 during the last 5 minutes of the experiment. There was no apnea at the end of the experiment.

The stomach of the animal was slightly distended at the end of the experiment. Corneal and light reflexes were present and very active. Three hours later the animal was on his legs and able to eat and drink. The next day the animal was normal and remained in good condition.

MECHANICAL RESUSCITATION

All students of asphyxia and resuscitation agree that the general term of "asphyxia" is a vague, confusing, and often misleading term. In fact, as it will be presently shown,

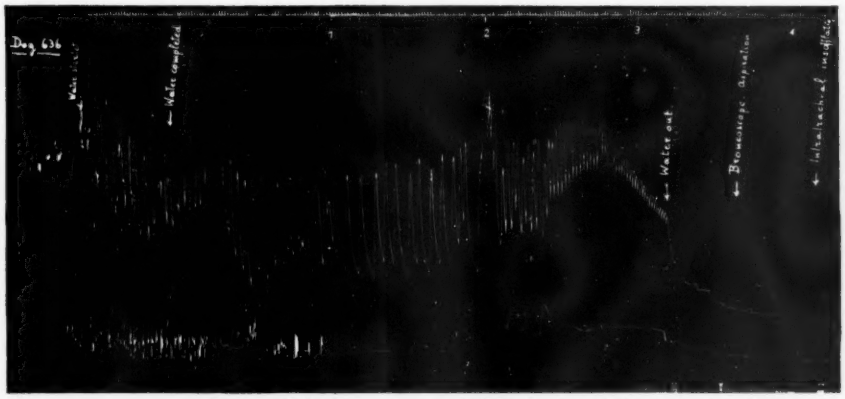


Fig. 11. Failure of attempt at resuscitation in submersion. The hood was removed at the end of the third phase. Blood pressure continued to drop. Bronchoscopic aspiration of fluid was applied 30 seconds after removal of hood, and intratracheal insufflation 30 seconds later without any result.

asphyxia, whatever its origin may be, is composed of four distinct phases which follow one another but they present different symptoms and different prognoses. Thus, for example, while resuscitation is very easy at the first and second phase, it becomes difficult at the beginning of the third phase, very difficult at the middle of this phase, and quite impossible at its end, and in the fourth phase. Therefore when the question of resuscitation is discussed and especially when the merits of the different procedures are appraised and compared, it is absolutely necessary to indicate with the greatest accuracy not only the phase but also the period of the phase of asphyxia in which the reported results were obtained. Reports and conclusions in which this point has not been strictly observed are deprived of any scientific value. I believe that is because this point has not been sufficiently stressed so far that so many contradictory opinions are held today upon the different methods of resuscitation. This contention is backed by our experimental data which are reported here.

The most commonly encountered forms of asphyxia belong to one of the following three groups: (1) Resistance to respiration, such as submersion in water, bronchial obstruction or combination of both as when the lung drowns in its own exudate; (2) vitiation of the respired air, such as oxygen want, or in breathing of anesthetic or neutral gas, or carbon monoxide poisoning; (3) disturbances of the respiratory center as in electric shock and possibly traumatic or postoperative shock.

It is not in the scope of this paper to enter into the details of resuscitation in all these forms of asphyxia. Thus resuscitation in carbon monoxide poisoning and of the newborn shall not be considered. I shall study asphyxia and resuscitation only as regards submersion, bronchial obstruction, and anesthesia—the forms of asphyxia of the greatest interest both to the thoracic surgeon and to the anesthetist.

Asphyxia by submersion. Asphyxia by submersion has been studied experimentally by means of a special technique which has rendered possible accurate and continuous recording of respiration and blood pressure throughout the entire duration of submersion. Flagg, Birnbaum, and I have devised a method during our studies on submersion which gave us valuable information. Our experimental findings were checked upon human cases of submersion which we had the opportunity to study on the beach of Coney Island during the summer of 1933.

Technique. Thirty-two dogs were used for these experiments, weighing around 10 pounds. The animals were anesthetized with sodium amytal, 10 per cent solution, injected intraperitoneally. Fifty-five milligrams per

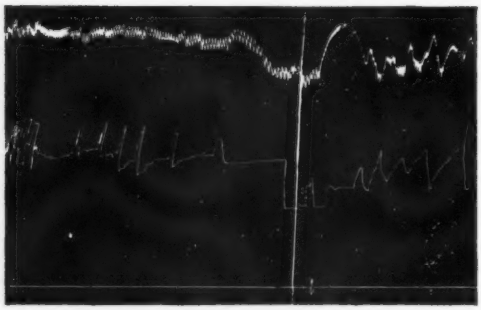


Fig. 12. Spontaneous resuscitation in submersion. The hood was removed 15 seconds before the end of the third phase.

kilogram of body weight was given. In a small number of dogs ether anesthesia was used instead.

The neck of the animal was shaved and anointed with petrolatum. A special hood had been constructed, of light metal, representing a cylinder 10 inches long and 6 inches in diameter. One base of this cylinder was closed with a diaphragm of rubber tissue in which a central opening was made. On the other base, a smaller and funnel-like cylinder was soldered. In the middle of the hood a hole was made which was closed, and kept water tight by a sheet of celluloid and served as an observation window. A pneumograph was applied on the chest of the animal and was connected with a recording tambour. The femoral artery was cannulated and the cannula was connected with a recording mercury manometer (Fig. 8).

By slightly stretching the opening of the diaphragm of the hood it was easy to pass through it the head of the animal down to its neck. Thus the head was contained in a cylinder the bottom of which was water-tightly fitted around the neck without exerting any undue pressure upon it.

Thus during the experiment it was possible to register on the smoked drum respiration, blood pressure, times in seconds and the oscillations of the resuscitation apparatus.

For producing asphyxia by submersion water was poured into the cylinder which was filled up until mouth and nostrils of the animal were completely under water. This technique rendered also possible the study of submersion in different medias. Interesting differences were noted when the animals were submerged in tap water, isotonic, or hypertonic salt solution. Moreover it was possible to interrupt instantly submersion or even to administer oxygen or carbon dioxide in oxygen by means of an intratracheal catheter while the mouth and nostrils of the animal were under water.

We shall report here the more interesting points of our findings.

Figures 9, 10, and 11 show the course of asphyxia by submersion in tap water. The whole phenomenon from its beginning to the death of the animal presented a remarkably constant duration of 4 to 5 minutes. This

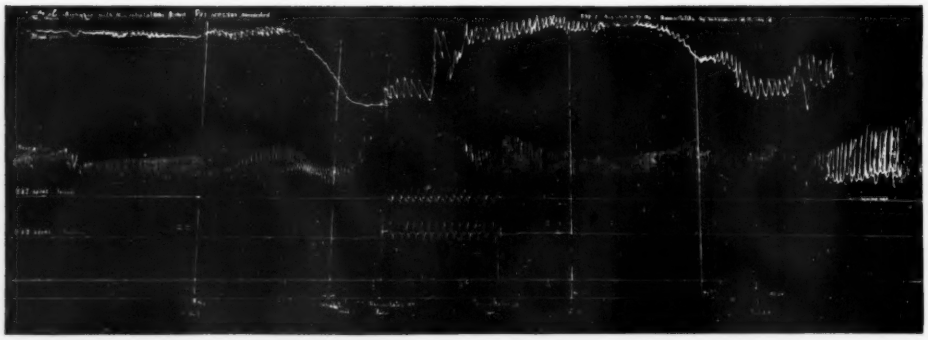


Fig. 13. Attempt at resuscitation in submersion, with E & J apparatus. End of third phase. Successful. The hood was removed at the end of the third phase. Manual artificial respiration was applied, *A. R.* without result. E & J apparatus was then used for 90 seconds with success. Blood pressure rose, spontaneous respiration resumed.

course was clearly divided into 4 distinct phases, each of 1 minute duration. These phases can be described as follows (Fig. 9).

The first phase is characterized by apnea and rise of blood pressure. This apnea is due to the reflex closure of the glottis. I shall call it the phase of initial apnea. Rise of blood pressure at the beginning of asphyxia is a constant phenomenon in all forms of asphyxia. The duration of this phase is of about 1 minute.

The second phase is characterized by labored respiratory movements and continuation of the rise of blood pressure. The animal fights for breath; the non-anesthetized animal is perfectly conscious until the end of this phase and fights vigorously to liberate itself of the hood. At the end of this phase, which lasts also 1 minute, consciousness disappears and tonic and clonic convulsions appear. This phase can be called the "phase of dyspnea."

The third phase is characterized by arrest of respiration, drop of the blood pressure, and disappearance of reflexes and muscular tonus. The duration of this phase is also of 1 minute. The animal which presented clonic and tonic convulsions at the end of the second phase, gradually relaxes and becomes limp, its jaw drops, the sphincters relax and the corneal and glottis reflexes disappear. I shall designate this phase as the phase of "terminal apnea."

The fourth phase is characterized by rapidly progressing weakness of cardiac contraction and arrest of the heart. I shall indicate this phase as phase of arrest of the heart. The same phases are seen in Figures 10 and 11.

The prognosis is very different in each of these phases; in fact when submersion is interrupted anywhere before the middle of the third phase immediate and spontaneous resuscitation always follows (Fig. 12); on the contrary, in the third phase (phase of terminal apnea) resuscitation which is still easy when submersion is interrupted at the beginning of this phase becomes increasingly difficult as we approach the end of this phase. Figure 11 illustrates this point. Although the hood was removed at the end of the third phase asphyxia progressed to the fourth phase and the heart stopped. Neither artificial respiration nor bronchoscopic intratracheal insufflation succeeded in resuscitating this animal.

The graph, Figure 13, is of considerable interest because it shows that resuscitation can be obtained in this phase by the use of the E & J apparatus when it is applied without any delay. The hood was removed at this experiment, as in experiment of Figure 11, at the end of third phase. Artificial respiration was without any response. On the contrary within 20 seconds after the application of E & J apparatus blood pressure rose almost vertically and the animal was brought back to life.

This experimental evidence shows clearly, I believe, the importance of dividing asphyxia by submersion into four phases. Moreover, it shows the futility of artificial respiration and carbon dioxide in oxygen inhalation beyond the third phase and the necessity of avoiding any loss of time by the immediate application of procedures which insure insufflation of oxygen

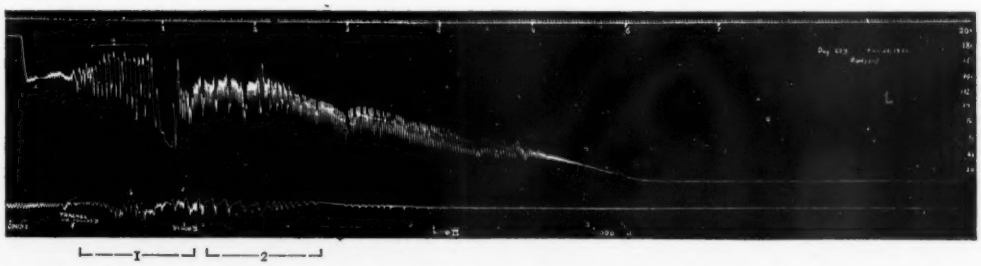


Fig. 14. Graph of asphyxia by obstruction of trachea in the dog, upper curve, blood pressure; lower respiration. In *1* the trachea was only partially obstructed; blood pressure was very slightly affected. At *2* obstruction was made complete. Blood pressure rose for 1 minute while respiratory movements became irregular—second phase. Then blood pressure began to drop and respiration ceased—third phase. Gradually heart stopped—fourth phase. Resuscitation was attempted without success at the fourth phase.

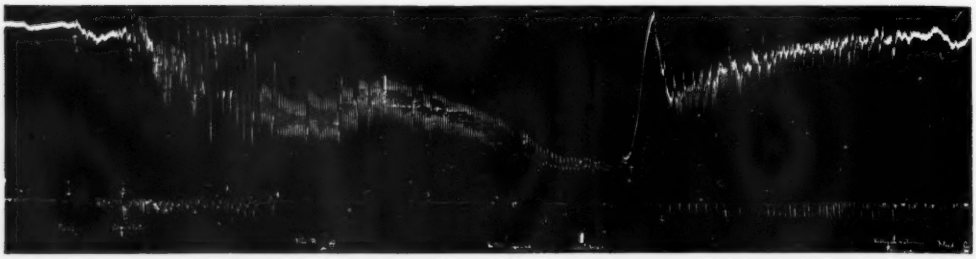


Fig. 15. Asphyxia by tracheal obstruction. Spontaneous resuscitation. Obstruction was removed at the end of third phase before the beginning of the fourth phase. It was found that the blood pressure rose immediately and that spontaneous respiration was resumed 20 seconds later.

into the lung. The fact that resuscitation is still easy at the beginning of the third phase while it is very difficult and often impossible at the end of the same phase and that the duration of this phase is of 1 minute only, shows clearly the paramount importance of time. Seconds count in asphyxia and often determine the life or death of the patient. This experimental evidence illustrates the statement previously made that unless the phase of asphyxia is accurately indicated in the results obtained with different procedures of resuscitation, no reliance can be placed upon the results reported.

The division of asphyxia into four phases is also evident in bronchial obstruction and in breathing of neutral or anesthetic gases (oxygen want).

Asphyxia by bronchial obstruction. Eighteen dogs were used for these experiments. Bronchial obstruction was obtained by introducing into the trachea, through the bronchoscope, a small balloon attached to a fine brass tube. This balloon could be inflated from the outside and this produced obstruction either of the trachea or of a common bronchus. The advantages of this technique are that complete obstruction can be obtained without any traumatism to the animal, that the degree of obstruction can be regulated at will and that it can be established or interrupted instantly.

The curve of asphyxia by complete obstruction of the trachea is very similar to the curve of submersion (Fig. 14). The four phases are clearly shown namely: initial apnea, dyspnea, terminal apnea, and arrest of the heart. Again the duration of each phase is of about 1 minute and death occurs within 4 to 5 minutes.

Removal of the obstructing agent before the end of the third phase is followed as a rule by immediate spontaneous resuscitation (Fig. 15). On the contrary, when obstruction is released later artificial resuscitation is generally necessary in order to obtain resuscitation (Fig. 16). In a general way, however, resuscitation is easier in bronchial obstruction than submersion. The reason is obvious; removal of the obstructing agent instantly establishes the patency of the air passages in uncomplicated bronchial obstruction while in submersion alveoli, smaller bronchi, and even larger bronchi may be filled with water. On the other hand, it should not be forgotten that there are cases of submersion in which very little water has penetrated into the lung, while, there are cases of bronchial obstruction in which the lung is filled up with bronchial secretions representing the "drowned-lung" of Leopold. These little known details explain the peculiar variations in resuscitation; they must be borne in mind in the appreciation of the causes of success or failure and of the therapeutic indications in each individual case.

Partial obstruction causes little changes in the curves of respiration and blood pressure (beginning of curve Fig. 14). It is surprising how little air is often sufficient to prolong life. This point is of paramount practical importance because it shows the necessity of insuring at once even partial patency of the upper respiratory ways. Suction of exudate present in the larynx, traction of the tongue and especially introduction of intratracheal catheter

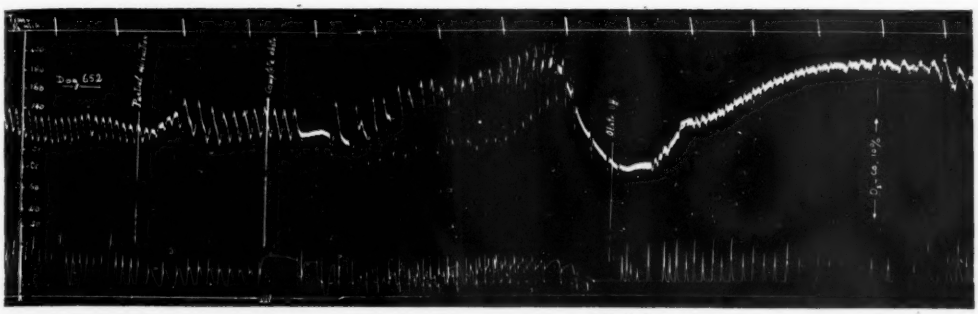


Fig. 16. Asphyxia by bronchial obstruction. Resuscitation by the E & J apparatus applied at the end of the third phase. From up down, times in ½ minutes, blood pressure and respiration. Obstruction of trachea was released at the end of the third phase. E & J apparatus was applied 20 seconds later. Blood pressure continued to drop for 30 seconds, it remained low for 30 more seconds, and then rose to slightly above normal.

when performed timely and skillfully, increase considerably the chances of resuscitation.

It is obvious that in asphyxia by tracheal obstruction or submersion, artificial respiration by the Shaeffer or Sylvester methods combined with carbon dioxide in oxygen inhalation will be successful as long as they are applied on patients with patent respiratory ways and before the end of the third phase. After this phase rhythmic insufflation and suction of air into the lung are incomparably more efficient. Figure 16 shows resuscitation obtained by the application of E & J apparatus, 1 minute after complete drop of the blood pressure, with heart beats hardly visible, that is almost at the fourth phase.

These two forms of asphyxia, by submersion and bronchial obstruction, are of great practical importance to the anesthetist and the thoracic surgeon. In fact, the great majority of deaths following thoracic operations for pulmonary suppuration are due to their combination. In these cases the patients die because of restriction of the respiratory field, with or without bronchial obstruction, by the bronchial exudate retained in the bronchial tree. From the evidence herein offered it becomes obvious that the only rational treatment in these cases consists in the rapid suction of this exudate by means of intratracheal catheter followed by rhythmic insufflation of carbon dioxide in oxygen, either by mouth-to-mouth insufflation or better by means of an apparatus. Moreover, preventive measures in these cases are of the greatest importance. Careful pre-operative removal of bronchial secretion by cough and postural drainage, and the use of intratracheal catheter during operation in all patients who expectorate over 30 cubic centimeters in 24 hours are lifesaving measures. It was shown elsewhere that aspiration of bronchial secretion before and after thoracoplasties in pulmonary tuberculosis have considerably decreased both morbidity and mortality in these cases.

Asphyxia by respiration of neutral or anesthetic cases. Asphyxia was produced experimentally by breathing of hydrogen, nitrogen, and helium. Seven dogs were used in these experiments; 2 with hydrogen, 2 with nitrogen, and 3 with helium.

The curves of these forms of asphyxia are identical with the curves of submersion and bronchial obstruction, with the only difference that the phase of initial apnea is less marked in them and occasionally absent. Figures 17 and 18 represent respectively the curves of asphyxia by overdose of ether and breathing of helium. Again we found in these curves as in the previous ones, the characteristic drop of blood pressure at the third phase followed by arrest of the heart within 5 minutes after the beginning of the experiment.

These two curves (Figs. 17 and 18) should be studied more closely because they show in a remarkable way, and for the first time as far as I know, the importance and efficiency of massage of the heart in resuscitation even

Fig. 17. Resuscitation in asphyxia by overdose of ether. Combined action of E & J apparatus and direct massage of the heart. *1*, fourth phase, arrest of the heart—6 minutes after respiratory arrest. *2*, E & J apparatus was put in action (2 minutes after arrest of the heart). Manual artificial respiration was without any effect. *M*, Direct massage of the heart, repeated at *M'* and *M''* followed by resuscitation, about 9 minutes and 50 seconds after complete arrest of respiration and 6½ minutes after arrest of the heart. (See text.)

over 10 minutes after complete arrest of the heart *provided that the lung had been maintained adequately ventilated.*

Resuscitation obtained after the fourth phase by combined mechanical pulmonary ventilation and massage of the heart. Two of these experiments are reported here.

Dog 18. Male, 13 kilograms. (Fig. 17). This dog was given ether until drop of blood pressure (third phase) had occurred and the heart stopped (fourth phase). E & J apparatus was applied 6 minutes after respiratory arrest, and 2 minutes after arrest of the heart. For 4 minutes no changes were noticed in the heart or the blood pressure. Nine minutes and 50 seconds after the onset of apnea and 6½ minutes after arrest of the heart, the abdominal wall was incised and the hand was introduced into the chest cavity; through the diaphragm the heart was grasped and massaged slowly. On the graph the massage was distinctly visible and is indicated by the letter *M*. Following the second massage of the heart a few cardiac contractions were felt which are seen on the graph. Following a third attempt the heart started beating regularly and vigorously. The animal was brought back to life.

Dog 19. Male, 18 kilograms. Anesthesia was effected with amytal, 10 per cent, intraperitoneally, 55 milligrams of amytal per kilogram body weight.

This animal was given pure helium to breathe (curve Fig. 18, A and B, 18B being the continuation of 18A). The animal entered the third phase 3½ minutes after the onset of the experiment and 1 minute later (4½ minutes after the onset of this experiment) there was terminal apnea and arrest of the heart. E & J apparatus was applied at the sixth minute. Rhythmic compression of the chest was used at same time without any effect upon heart. At the eleventh minute (6 minutes after apnea and 5 minutes after arrest of the heart) a long abdominal incision was made and the hand was introduced into the chest through an opening made in the diaphragm. Seven times the heart was massaged, once every minute at the eleventh, twelfth, thirteenth, fourteenth, sixteenth, seventeenth, and eighteenth minute. Each time there was a response of the heart, which was becoming progressively stronger and longer, as it is clearly shown in the graph. At the twentieth minute (15 minutes after arrest of the heart) the heart started beating again, blood pressure rose and spontaneous respiratory movements were re-established.

These two experiments show that massage of the heart as a method of resuscitation in desperate cases of asphyxia may be successful, provided that the pulmonary blood had been maintained adequately ventilated. It is my contention that pulmonary ventilation is a compulsory factor for the success of massage of the heart. It is reasonable to admit that unless the blood pumped into the heart and forced into its coronary vessels by massage of this organ be adequately oxygenated, no resuscitation of this organ can take place.

These experiments are of considerable practical importance. They prove that massage of the heart should be accepted as a legitimate procedure for resuscitation; moreover that immediate application and continuation of mouth-to-mouth or mechanical

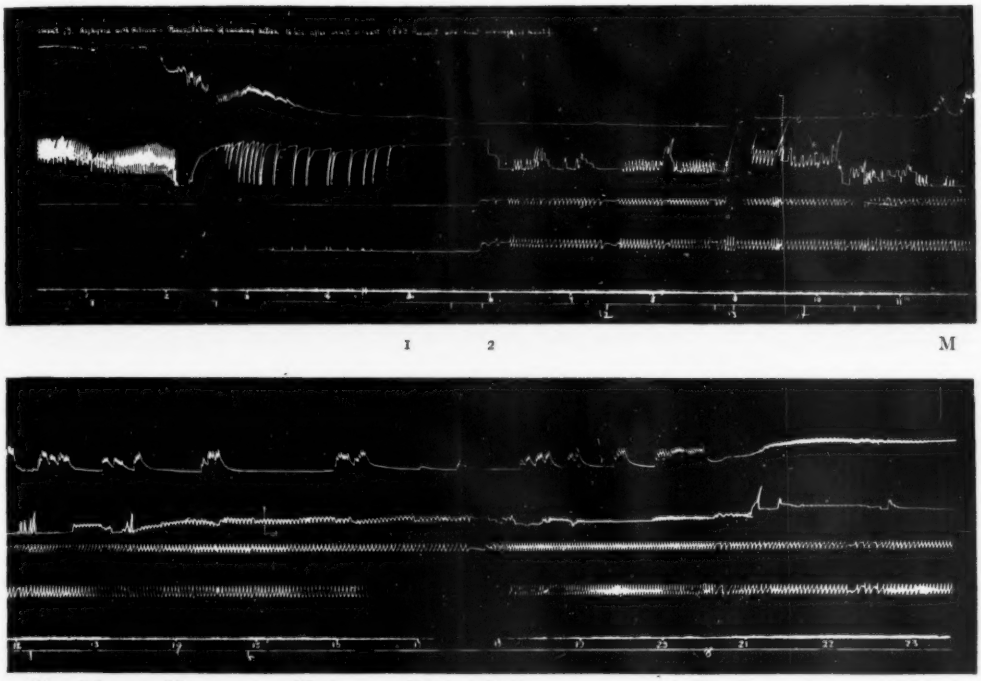


Fig. 18 A and B. B, the continuation of B. Resuscitation in asphyxia by helium. Combined action of E & J respirator and direct massage of the heart. Arrest of the heart at the fifth minute, *1*. Respirator was put in action at the sixth minute, *2*. *M. M.*, massage of the heart, each massage being followed by a faint response of the heart. At 3, 15 minutes after arrest of the heart spontaneous beats had resumed and blood pressure rose. (See text.)

insufflation gives enough time to surgeon to enter into the chest either through the abdominal cavity or through the fourth intercostal space, with all aseptic precautions. If my interpretation of data presented is correct, massage of the heart should be recognized not only as a legitimate procedure but as a compulsory one in advanced cases of asphyxia.

Action of E & J apparatus in open chest operations. The behavior of dogs, with wide open chest, in which respiration was insured by the resuscitator was investigated in 13 animals. On these animals were performed ligations of the pulmonary vessels, lobectomies, pneumonectomies, wrapping of lobes in rubber bags for the production of compressive atelectasis and ligature of the coronary vessels. All these animals resumed normal respiration after closure of the chest.

It must be noted that these operations were carried out in the dog with greater ease than with ordinary intratracheal insufflation because relatively slight expansion and retraction of the lungs were sufficient to insure adequate ventilation; thus the chest was not crowded by over expanded lungs and there was more room for the performance of the operations.

The following experiment illustrates that by using the E & J apparatus dogs can remain for a long time with the chest widely open without showing any marked disturbances of respiration and circulation; when the chest was closed the animal immediately resumed normal respiration.

Experiment 33. Dog weighed 8 kilograms. Anesthesia given was amytal intraperitoneally. Chest was opened by section in the middle of the sternum;

ligation of bleeding vessels and wide retraction of the edges of the sternum by means of self-retaining retractor. Mask connected with resuscitator. Resection of the right lung. After 2 hours, the chest was closed in an air-tight manner by means of clamps and resuscitation was discontinued. Spontaneous respiration was immediately resumed and the blood pressure rose.

Possibility of injury to the lung by positive intrapulmonary pressures. In order to investigate this point we used lungs of dogs removed immediately after death with care to prevent any injury to them. Manual handling of the lung was avoided. The lungs were separated from the heart after ligation of the pulmonary arteries and veins. The two tubes of the resuscitator were connected with a Y tube the vertical branch of which was solidly tight to the trachea as was the rubber bag in Figure 2. Under the action of the resuscitator the lung expanded and retracted rhythmically; with positive pressure of 14 millimeters of mercury it became only moderately distended. In order to produce rupture to the lung it has been necessary to connect the trachea directly with the faucet of compressed air of the laboratory; the lung was placed and maintained under water by a metallic net placed above the lung; rupture of the lung and bubbling of air appeared only when the pressures reached between 52 to 58 millimeters of mercury. It is therefore impossible that a positive pressure of 14 millimeters of mercury can cause even the slightest traumatic lesion of the lung. On the contrary, when there is an advanced degree of collapse, as there is 5 to 10 hours after death of the animal, the lung can be only partially inflated by the positive pressure built by this apparatus. Therefore, it is reasonable to believe that clinically we may encounter collapsed lungs resisting adequate expansion with 14 millimeters of mercury positive pressure. For this reason we have advised the manufacturer to add a fool-proof valve which could allow, when and if necessary, intermittent insufflations under a positive pressure of 20 to 30 millimeters of mercury.

It is true, however, that high positive intrapulmonary pressures above 50 millimeters can produce rupture of pulmonary alveoli, often complicated by mediastinal and subcutaneous emphysema, pneumothorax, and even pneumoperitoneum. Intrapulmonary hemorrhage and cardiac or cerebral air embolism may also be produced by high intrapulmonary pressures.

Ewald and Kobert (1883) had found that in rabbits when the pressure in the lung reached 40 millimeters of mercury, air could be detected in the abdominal cavity. Joannides (1931) produced pneumothorax, pneumoperitoneum, and even air embolism with intrapulmonary pressures of from 50 to 100 millimeters of mercury.

Polak and Adams (1932) have carried out a series of interesting experiments in dogs, in which arterial and venous pressures were recorded. They have introduced air under pressure into the trachea through a tracheal cannula. A special cannula was interposed in the carotid artery filled with normal saline, which was arranged to act as a trap for any air bubbles which might be present in the blood or the artery. When they raised the intrapulmonary pressure to 60 millimeters of mercury for 10 seconds they observed the typical fall of arterial pressure and rise of venous pressure, already described (Figs. 4 and 5). No air bubbles appeared in the carotid trap with 60 millimeters of mercury pressure. Only when the intrapulmonary pressure was brought to 80 millimeters of mercury and maintained at this level for 10 seconds, numerous air bubbles appeared in the carotid trap. With 100 millimeters of mercury for 10 seconds still more air appeared in the carotid trap and the animal ceased to breathe though the heart continued to beat for 2 more minutes. At autopsy, besides extensive mediastinal and subcutaneous emphysema, interstitial emphysema was present around the pulmonary vessels and hemorrhagic areas were seen extending into the lung substance. Microscopically, vascular hemorrhages were found in the lung and air emboli were present in the coronary and mesenteric arteries and in vessels of the brain. Air was present in both ventricles. From their numerous experiments these authors concluded that no harm can be caused as long as the intrapulmonary pressure remains below 80 millimeters of mercury. But from 90 millimeters of mercury or more traumatic air embolism is likely to occur.

These experiments of Polak and Adams were carried out in order to explain embolism occurring in sailors carrying the submarine escape respiratory apparatus and rapidly rising from a depth of 15 feet or more. Haldane, commenting on their work said: "When a man comes up rapidly from a depth of even as little as 15 feet, with his mouth closed and without breathing, excess of intrapulmonary pressure over external pressure is built and it rises rapidly to a high figure. As soon as this pressure exceeds about 80 millimeters of mercury there is stretching and tearing of alveoli and their capillaries with the result that air is forced into these vessels; nothing of the kind occurs if the man is instructed to breathe during the ascension."

Therefore, we can conclude that no traumatism to the lung is possible even when positive pressures of 30 and 40 millimeters of mercury are used. It is fortunate that there is such a large margin of safety between the pressures necessary and sufficient for resuscitation and the pressures which are liable to cause rupture of alveoli; thus the lung may be forcibly expanded if it presents an advanced degree of collapse without any danger of injury.

In the light of the experimental evidence presented here I was forced to revise my previous unfavorable opinion of the automatic pulmotor principle. This opinion was based upon the conclusions of the reports in 1913 of the Commission of Resuscitation from Electric Shock (17) and of the Committee on Resuscitation from Mine Gases (18) in 1914. These conclusions were both edited by the secretary of this committee, Yandel Henderson. This author in numerous papers which have appeared since the publication of these reports has repeatedly and insistantly expressed his distrust for all procedures of resuscitation based upon the principle of the automatic pulmotor of Draeger. I cannot agree with this author. The experimental work, only partially reported in this paper, has convinced me that the E & J apparatus is harmless and of great help in resuscitation. Therefore I thought that I was authorized to apply it to patients. This trial has justified my favorable opinion, as it is shown in the reports of a small number of human cases.

HUMAN CASES

This apparatus was used on 12 patients during or following operations for pulmonary suppuration. All had shown advanced asphyxia with apnea. The histories of 3 cases, 2 successful and 1 failure, are given here. A more extensive study of all cases will be given later in a special paper.

CASE 1. S. M., aged 28 years, white, female, was admitted to Sea View Hospital, January 15, 1935; readmitted June 9, 1936. No. 11466–36. Diagnosis: right mixed infection tuberculous empyema; drained; left pneumothorax with adhesions. Sputum, Gaffky No. 3.

November 24, 1936. Pneumonolysis of left apex. Successful. Sputum turned negative for 2 months.

December 29, 1936. First stage thoracoplasty on right side. Total resection of three ribs. Cyclopropane anesthesia. Good recovery.

April 6, 1937. Second stage thoracoplasty, resection of fourth, fifth, and sixth ribs. Cyclopropane anesthesia. Patient strongly anoxemic. Vital capacity 950 cubic centimeters. Intratracheal catheter was used.

Twenty minutes after beginning of operation patient became extremely cyanotic with shallow, rapid, and periodic breathing. Patient was given carbon dioxide in oxygen inhalation which improved her condition. At the end of the operation condition became worse—gray cyanosis, with shallow, irregular, and gasping breathing; fall of blood pressure—pressure could not be recorded in the sphygmomanometer. Heart was irregular. Stimulants and carbon dioxide in oxygen inhalation were without any effect. Suddenly respiration stopped, eyes were glassy, pupils half dilated and jaw relaxing.

Resuscitator was applied and kept on for 15 minutes. Immediate and striking improvement was noticed. Within 5 minutes heart beats became regular, pulse could be felt in the radial artery (140 per minute) and cyanosis cleared up considerably. Spontaneous breathing was re-established within 12 minutes. Resuscitation was stopped after 14 minutes. Patient made uneventful recovery.

CASE 2. H. L., white, female, aged 23 years, with bilateral thoracoplasty was admitted at Sea View Hospital June 4, 1936. No. 1316–36. Bilateral ulcerative pulmonary tuberculosis. Sputum, Gaffky No. 6.

Pneumothorax was attempted on both sides without success. Vital capacity 1200 cubic centimeters. Marked chronic anoxemia.

December 22, 1936. First stage thoracoplasty was done on left side, with cyclopropane anesthesia; resection of five ribs. During operation patient had repeated attacks of apnea but recovered with inhalation of carbon dioxide in oxygen and rhythmic pressures on the chest.

At the end of the operation respiration became very shallow and hardly noticeable; marked cyano-

sis; blood pressure fell rapidly and could not be recorded; respiration ceased. Patient was in profound shock and complete relaxation. Heart beats could not be detected.

Mouth-to-mouth insufflation was instituted and resuscitator was applied. Within 7 minutes color improved, blood pressure rose to 85 millimeters systolic and spontaneous respiratory movements were resumed. Inhalation of carbon dioxide in oxygen was then continued for 40 minutes until patient was awakened. Recovery was uneventful.

February 23, 1937. First stage thoracoplasty on right side, with cyclopropane anesthesia; resection of four ribs. No shock. Course uneventful.

CASE 3. W. A., white, aged 34 years. Patient was admitted at Sea View Hospital July 31, 1936. No. 13941–36. Diagnosis: bilateral ulcerative pulmonary tuberculosis.

January 22, 1937. First stage thoracoplasty with resection of three ribs and apicolysis. Cyclopropane anesthesia was used. Postoperative course was smooth.

January 28, 1937. Sixth postoperative day: spontaneous pneumothorax on right side. Deflation of 1100 cubic centimeters of air with marked relief. Patient was placed on continuous deflation.

February 1, 1937. Right lung partially re-expanded. The patient who had been comfortable for the last 3 days, suddenly developed pain in left chest and extreme dyspnea with cyanosis. Diagnosis of obstruction of the left lower lobe was made in the x-ray film. An intratracheal catheter was introduced and the right lower bronchus was aspirated. Patient was improved immediately.

February 4, acute episode similar to that on February 1, occurred. An intratracheal catheter was introduced in the left bronchus and 20 cubic centimeters of thick mucus was aspirated. Patient was immediately improved. However, 1 hour later a new attack of extreme dyspnea occurred, and when the resident physician arrived a few minutes later (no more than 5 to 7) patient was in apnea, heart beats could not be elicited, pupils were dilated and lower jaw relaxed. Intracardiac adrenalin was given and mouth-to-mouth insufflation was instituted until the apparatus was brought in. Within 2 minutes after application of apparatus heart beats could be heard again but they were very rapid and faint. Bronchial suction was repeated, but during suction heart stopped again. Apparatus was re-applied and heart beats were established again. Occasional spontaneous respiratory movements were produced. After 30 minutes heart went into fibrillation and patient died. Direct massage of the heart through abdominal incision could not be resorted to because of lack of authorization. Patient died 1 hour and 40 minutes after last attack. At the autopsy no other cause of death was found outside of advanced atheroma of aorta. Right auricle and ventricle were moderately dilated and left heart hypertrophied.

These cases are typical examples of advanced forms of asphyxia with apnea in the presence of marked chronic anoxemia. In all these cases resuscitation began after the third phase. The results obtained show the importance, in such cases of immediate and energetic resuscitation, and the futility of simple inhalation with manual artificial respiration. In these cases the insufflation—suction apparatus and mouth-to-mouth insufflation—are the only methods which have given me satisfactory and often striking results.

SUMMARY AND CONCLUSIONS

The relatively frequent development of acute asphyxia complicating chronic anoxemia, always present in cases with chronic pulmonary suppuration, either during operations upon these cases or during the postoperative period, has rendered necessary the perfection of our procedures of resuscitation.

A long study, clinical and experimental, was carried out on dogs, on humans drowned at Coney Island beach, and on our patients operated upon for chronic suppurations of the lung, especially with advanced pulmonary tuberculosis and bronchiectasis.

Ample experimental evidence has shown that acute asphyxia should be divided into 4 phases. It was shown that during the first 2 phases and the beginning of the third, resuscitation can be easily obtained with manual artificial respiration and inhalation of oxygen-carbon dioxide, 5 to 10 per cent as shown by Yandel Henderson. On the contrary, in the third phase which is characterized by rapidly falling blood pressure ending in arrest of the heart (fourth phase), inhalation and manual methods are inadequate to insure resuscitation. Suppression of muscular tonus and apnea prevent any adequate ventilation of the blood by these methods.

Experience had shown that in these cases mouth-to-mouth insufflation has given by far the best results. Therefore, it was thought that an apparatus based on the automatic pulmotor principle, with constant pressures and variable volumes, could be useful in cases in which mouth-to-mouth insufflation was not applicable as in tuberculous or bronchiectatic patients.

An apparatus based on this principle was

selected (E & J apparatus) and submitted to exhausting experimental investigation. The results of this inquiry having been favorable, this apparatus was used upon human cases with satisfactory results.

It seems, therefore, that previously prevailing opinions against the principle of a rhythmic insufflation-aspiration must be revised. At any rate these opinions were not based, at least in the reports and papers published up to this date, upon any thorough experimental or even clinical evidence. On the other hand, it is peculiar that even in the papers of Henderson in which the principle of insufflation-suction is definitely condemned, intratracheal insufflation (procedure of Meltzer) is recommended for the resuscitation of stillborn infants.

The evidence presented in this paper has convinced me that while manual artificial respiration with oxygen-carbon dioxide inhalation are efficient procedures for non-advanced degrees of asphyxia (first to third phase) they become useless and even dangerous, because of loss of time, when asphyxia has reached the third and especially the fourth phase. In the presence of apnea and beginning relaxation of the muscular system, only methods insuring forcible insufflation of oxygen into the lungs can still produce resuscitation.

It should be understood that these two procedures should not be opposed to each other. They have their special indications and they complete one another. The automatic pulmotor principle, complements manual artificial respiration with inhalation in advanced asphyxia as the principle of passive expansion-contraction of the chest, utilized in the machines of Drinker and Emerson, is the only one suitable in cases of paralysis of the respiratory muscles.

In a general way mouth-to-mouth insufflation or mechanical insufflation-suction need be applied for a relatively short time and until spontaneous respiratory movements have been resumed. Resuscitation should be continued thereafter by the inhalation method until complete recovery. In cases of asphyxia with carbon monoxide, inhalation should be continued for a relatively long time.

Thus we come to the conclusion that the ideal mechanical contraption for resuscitation is an apparatus which combines an inhalator and a resuscitator. A simple inhalator represents only one half of such an apparatus. Therefore I am satisfied that the E & J apparatus is of a great help in mechanical resuscitation.

It is also my contention that this apparatus can cause no harm in the hands of non-medical but trained rescue squads. The fear of causing pulmonary, cardiac, or respiratory complications by rhythmic rise and fall of intrapulmonary pressure had not been corroborated either by my experimental and clinical investigation or by the studies of other authors.

Moreover, it was shown in the course of this work that in cases of asphyxia with apnea and arrested heart, resuscitation is possible by direct massage of the heart within 10 minutes from the time of arrest of the heart, provided that the lungs have been maintained actively ventilated.

Yandel Henderson has said recently that much still remains to be learned about asphyxia. It can be added to this wise remark that in order to learn it is necessary to free ourselves from cumbersome dogmatism and preconceived ideas. Only thoroughly checked experimental evidence and equally thoroughly controlled clinical facts must guide us in our statements and conclusions. Asphyxia has entered today the domain of everyday practice and its fundamentals should be well understood by anesthetist, surgeons and physicians, and adequate equipment for resuscitation should be made available for timely use.

BIBLIOGRAPHY

1. Bernard, Claude. Lessons sur les phénomènes de la vie. Paris, 1893.
2. Bert, Paul. La pression barométrique. Paris, 1878.
3. Bohr, C. Skandin. Arch. f. Physiol., 1891, 2: 236; 1905, 17: 104; 1909, 22: 221.
4. Chillingworth, F. P., and Hopkins, R. Am. J. Physiol., 1930, 51: 289.
5. Coryllos, P. N. Etiology, prevention and treatment of postoperative hemorespiratory complications in the surgical treatment of pulmonary tuberculosis. J. Thoracic Surg., 1933, 2: 384.
6. Idem. Pathologic physiology of the tuberculous lung. Goldberg's Clinical Tuberculosis. Philadelphia: F. A. Davis, 1935.

7. EWALD, J. R., and KOBERT, R. Arch. f. d. ges. Physiol., 1883, 31: 160.
8. HALDANE, J. S., and PRIESTLEY, J. G. Treatise on Respiration. (New Edition.) New Haven: Yale University Press, 1935.
9. HENDERSON, Y. Resuscitation. J. Am. M. Ass., 1934, 103: 750; 834. Fundamentals on asphyxia. J. Am. M. Ass., 1933, 101: 261.
10. HERING, E., and BREUER, J. S. B. Akad. Wiss. Wien., 1868, 57: 672; 1868, 58: 909.
11. JOANNIDES, N. Arch. Int. Med., 1931, 47: 196.
12. KATZ, S. Ztschr. f. Biol., 1909, 52: 236.
13. KEITH, A. The Mechanism of Respiration in Man, Further Advances in Physiology. London: Edward Arnold, 1909.
14. LUDWIG, G. Z. Ges. Aertze Wien. 21. 1. 145. 1865 (Quoted in Haldane).
15. MEAKINS, J. C., and DAVIES, H. W. Respiratory Functions in Diseases. Edinburgh: Oliver Boyd, 1925.
16. POLAK, B., and ADAMS, H. Nav. Med. Bull. Wash., 1932, 30: 165.
17. Report of the Commission on Resuscitation from Electric Shock. National Electric Light Association New York, 1913.
18. Report of the Committee on Resuscitation from Mine Gases. Washington Government Printing Office. Technical Paper 77.
19. ROST, E. Beitrag zur Kenntnis der Kreislaufverhaeltnisse bei Wiederbelebung durch Veraenderung des intrapulmonares Druckes. Ztschr. f. d. ges. exper. Med., 1932, 82: 17.
20. WATERS, R. M., and BENNET, J. H. Artificial respiration, etc. Anæs. & Anal., May-June, 1936.

THE FERTILE PERIOD IN PRACTICE

A Five-Year Clinical Study

ARTHUR G. MILLER, B.S., A.M., M.D., Hobart, Indiana

IT is not my purpose in this article to enlarge the ever-increasing amount of technical data that are constantly broadening and changing our viewpoint of the phenomena of ovulation, conception, and pregnancy. But the avenues of thought, study, and research opened by work already accomplished are fascinating in the extreme, and the dimly seen possibilities of outstanding service to humanity urge every scientifically minded physician to add his bit to the still obscure phases of the problem.

Most of us cannot carry on the necessary research or laboratory and clinical procedure and I am, therefore, encouraged to note my own experience in actual practice, in the belief that every doctor can use some of the results of my more-or-less pioneering clinical efforts with the assurance of a successful outcome in practically all cases.

My interest in the fertile period and the physiological and biological discoveries that pointed to its existence began during a period of study in the Vienna clinics in 1931. There I first became acquainted with the work of Aschheim and Zondek, Ogino, Knaus, and others. Upon my return I began the regular use of the Aschheim-Zondek test for pregnancy, and developed a single injection method, using rabbits for test animals. This work was described in an article in *Medical World*, August, 1933. These efforts led to consideration of the fertility-sterility theory, which I hesitated to accept fully because I could not satisfy myself that the observed phenomena were based on a rational thesis.

INVESTIGATION OF THE SCIENTIFIC BASIS

In this quandary I began a thorough study of existing literature, including the latest and most pertinent data on the sperm cell, the egg cell, the ovary and the corpus luteum, and the uterus and the pituitary hormones. The work of many investigators on the lower mammals, from the mouse to the monkey, was reviewed and verified. Nothing was taken for granted.

With the aid of Professor Thomas of the department of physics, Valparaiso University, hormones were extracted from female urine, and their action tested upon laboratory animals. Also with the technical aid of Professor Thruen of the chemistry department and Professor Elliot of the biology department, Valparaiso University, and the very generous help of the Methodist Episcopal Hospital, Gary, Indiana, the work of both Drs. Ogino and Knaus was repeated and checked.

There gradually appeared a rational premise for the existence of a fertile period in the menstrual cycle, and this was supported by all of the carefully verified evidence. It seemed advisable, therefore, to make actual tests and I commenced the application of the theory in a few cases, using the time intervals suggested by Knaus. The results of these efforts were most encouraging and were described by my associates and myself in SURGERY, GYNECOLOGY AND OBSTETRICS, June, 1933.

FIVE HUNDRED INDIVIDUAL CASES TESTED

From these early beginnings to the present time I have utilized the fertile period procedure in 500 private cases with excellent results. From time to time I have instituted such corollary procedures and changes as seemed necessary, and have tested various calendars and time interval indicators, by which the patient may locate her own fertile periods under my supervision. The procedure has been used in some instances to avoid pregnancy; in others to bring about pregnancy; and in many to space pregnancies properly.

Of these 500 women, 20 were considered unfit to apply the fertile period knowledge,

From the Miller Clinic.

TABLE I.—LOCATION OF OVULATION BY SYMPTOMS

Previous menstruation	Ovulation symptoms		Following menstruation	Interval—days	Length of cycle—days
	Location	Date			
12- 1-35	Right ovary	Dec. 14	Dec. 28	14	27
12-28-35	Left ovary	Jan. 13	Jan. 27	14	30
1-27-36	Both ovaries More on right	Feb. 13	Feb. 27	14	31
2-27-36	Left ovary	Mar. 16	Mar. 30	14	32
3-30-36	Right ovary	Apr. 14	Apr. 28	14	29
4-28-36	Left ovary	May 14	May 28	14	30
5-28-36	Right ovary	June 11	June 25	14	28
6-25-36	Left ovary	July 8	July 22	14	27
7-22-36	Both ovaries More on right	Aug. 7	Aug. 21	14	30
8-21-36	Left ovary	Sept. 7	Sept. 21	14	31
9-21-36	Right ovary	Oct. 9	Oct. 23	14	32
10-23-36	Left ovary	Nov. 7	Nov. 21	14	29
11-21-36	Right ovary	Dec. 8	Dec. 22	14	31

their condition being determined by a simple procedure which is followed in each case: (1) each woman is required to present a written record of the beginning dates of the last six menstruations; (2) each woman is given a thorough physical examination which includes a pelvic search for pathology.

IMPORTANCE OF PHYSICAL EXAMINATION

The physical examination is just as important as the menstrual record, because a woman may have a seemingly normal cycle variation and yet be afflicted with some systemic or pelvic condition which will soon make it impossible for her to use the fertile period law successfully. This careful weeding out of the abnormal cases accounts in a large measure for the very gratifying results obtained in this study, as compared with the many failures reported by other women who have attempted to apply the new knowledge without the advice and guidance of their physicians.

The 20 abnormal women showed the following conditions: 3 had well advanced pulmonary tuberculosis; 4 had a fibroid uterus; 1 had an ovarian carcinoma; 4 had cervical carcinoma; 2 had occluded fallopian tubes; 4 had large ovarian cysts; 1 had a uterine polyp; and 1 had pernicious anemia.

PHYSIOLOGICAL FACTS LOCATE FERTILE PERIOD

The existence of definite fertile and sterile periods in the menstrual cycle is based on just three facts: (1) Ovulation occurs 14 days before the following menstruation. (2) The egg cell can be fertilized only during the 12 hour period immediately following its emergence from the follicle. (3) The fertilizing ability of the sperm cell in the female genital tract is maintained for not more than 24 to 36 hours.

Much research remains to be done to determine these intervals exactly under all kinds of conditions. For example, no free fertilized human egg has ever been removed from the uterus of a woman, the youngest embryo yet described being 11 days old.[1]

However, if the intervals herein noted are assumed to be the maximum, it is possible to calculate the location of supposedly sterile periods, which can then be tested for various cycles. This has been the basis of my 5 year study.

OVULATION INDICATED BY SYMPTOMS IN SOME CASES

Many women observe a painful sensation over one or both ovaries for an hour or more at the time of ovulation. Late in 1935 I asked one of my patients who always recognizes the *mittelschmerz* to keep a record of the date and location of these pains, as well as the menstruation dates. Her record is shown in Table I. This woman is in normal health, 32 years old, and has two children. She knows nothing about the time when ovulation is supposed to occur. She describes her symptoms on the dates shown as similar to those at the onset of menstruation. The record is valuable as corroborating evidence that ovulation occurs 14 days before the following menstruation. We have found, however, that most women cannot locate the day of ovulation accurately from symptoms.

FERTILE PERIOD LOCATED BY OVULATION

For the location of the fertile period the day of ovulation is the basis. As already stated, ovulation occurs 14 days before the following menstruation. Figure 1 shows the position of

[1]Research along this line is now being conducted in this clinic.

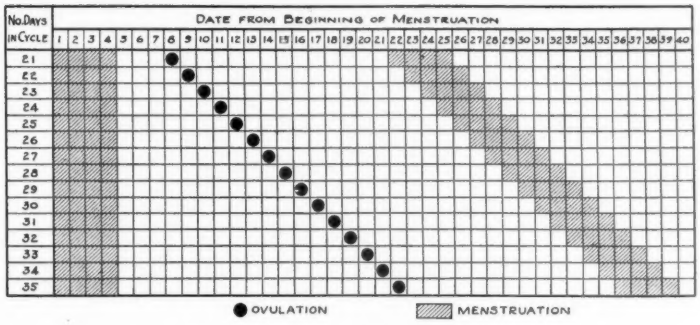


Fig. 1. Ovulation date for various cycles.

the day of ovulation in various cycles ranging from 21 to 35 days in length. In all of my work I have used a 5 day fertile period for a given cycle. This includes the day of ovulation as the fertility period of the egg cell, and 2 days preceding the day of ovulation as the fertilizing life span of the sperm cell. A day is then added at the beginning and end of this 3 day period to allow for the variation of a fraction of a day in the actual time of ovulation. The fertile periods for a number of cycles are shown in Figure 2, the day of ovulation being the next to the last day of the fertile period in each case.

In the present state of our knowledge the only exact measure of the length of the menstrual cycle is its termination, the onset of the next menstruation, and the beginning of the next cycle. If it were necessary to wait for this occurrence the information would be just 2 weeks late, and the only woman who could apply the fertile period knowledge would be one with the uniform cycle, having the same number of days each month. Such women are apparently very rare indeed.

THE LAW OF CYCLE VARIATION

Accurate study of the menstrual cycles of many women has revealed, however, that there is a law of recurrence in their cycles. This law may be expressed as follows: *Barring accident or disease, the menstrual cycle of a normal woman varies in length continually between a certain maximum and minimum number of days.* Here is the key that opens the door to the location of the ovulation date within a certain period, thus pointing out the location of a period of possible fertility in the cycle of a normal woman.

The longest and shortest cycles shown by the written record, kept for 6 months or more, determine the length of the period of possible fertility. For instance, if the shortest cycle is 26 days and the longest cycle is 30 days, ovulation may occur on the thirteenth, fourteenth, fifteenth, sixteenth, or seventeenth day of the cycle, as shown in Figure 1. Allowing 3 days before the first ovulation date and 1 day after the last ovulation date, the period of possible fertility is from the tenth to the eighteenth day, inclusive. All the remaining days of the cycle are sterile. Figure 3 shows the periods in the 26 to 30 day cycle graphically.

NORMAL CYCLE LENGTH AND VARIATION

In the 480 normal patients who form the basis of this study the first thing of interest is the cycle length and its variation. Table II shows that these women had individual cycle variations of from 1 to 9 days. The numbers of cases for each variation follow the "normal distribution" type of curve, as would be expected, the variation norm probably lying between 4 and 6 days. The rarity of the uniform, unvarying cycle, as well as the variation of 10 days or more, is definitely indicated. The fact that about 85 per cent of these women had a variation of not more than 6 days (11 day fertile period) is also of interest.

The lower limits of the cycle lengths are listed in Table III. It will be noted here that

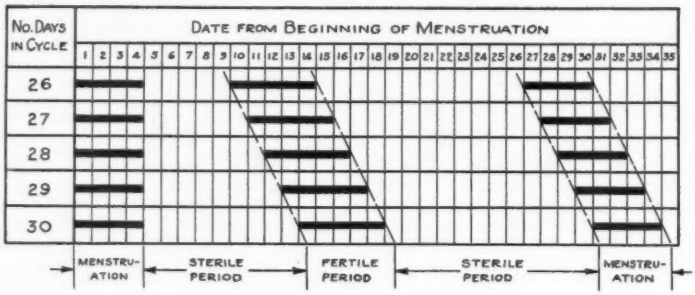

No. Days in Cycle
Date from Beginning of Menstruation
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35
26
27
28
29
30
Menstru-ation
Sterile period
Fertile period
Sterile period
Menstru-ation

Fig. 2. Fertile period for various cycles.

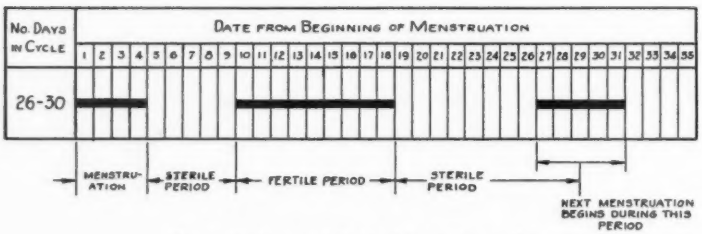

No. Days in Cycle
Date from Beginning of Menstruation
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35
26-30
Menstru-ation
Sterile period
Fertile period
Sterile period
Next menstruation begins during this period

Fig. 3. Various periods in 26 to 30 day cycles.

the numbers of cases do not follow the "normal distribution" curve, since a majority of these women had a minimum cycle length of 26 days.

Table IV lists the maximum cycle lengths. Here the numbers of cases again seem to follow the normal distribution, with the maximum cycle length norm lying between 30 and 32 days. The data listed in Tables II, III and IV are shown graphically in Figure 4, which gives a fairly definite picture of what the physician can expect among his normal, healthy patients. It shows that the old, time honored 28 day cycle has been largely a figment of the imagination, and that the average healthy woman will have a cycle which varies between a minimum of 26 or 27 days and a maximum of 30 to 32 days.

The implications of these figures are extremely fascinating because they point to the possibility of using the accurate record as an indicator of abnormal female condition. I have explored this possibility and in a number of cases have been able, through careful study of the menstrual record and a subsequent examination, to detect incipient disorders of which the patients were entirely unaware.

IMPORTANCE OF MENSTRUAL RECORD IN DIAGNOSIS

It is my belief that an accurate menstrual record is a definite indicator of normal or abnormal function and that a more concerted effort should be made by members of the medical profession to secure accurate, authentic menstrual histories. Heretofore, most of the published records have come from the inmates of hospitals and other institutions and were based entirely on memory. Little attention has been paid to the physiological and pathological conditions of the women in relation to the menstrual flow. What we need is a great mass of data from women in all walks of life; from the normal, healthy ones, as well as those who suffer from incipient or advanced abnormal conditions.

CONCEPTION CONTROLLED SUCCESSFULLY

A most significant fact about this 5 year use of the fertile period procedure is that not a single pregnancy has resulted from cohabitation outside the fertile periods established for the various patients. A total of 12 women who desired to avoid pregnancy have become pregnant through cohabitation during the fertile

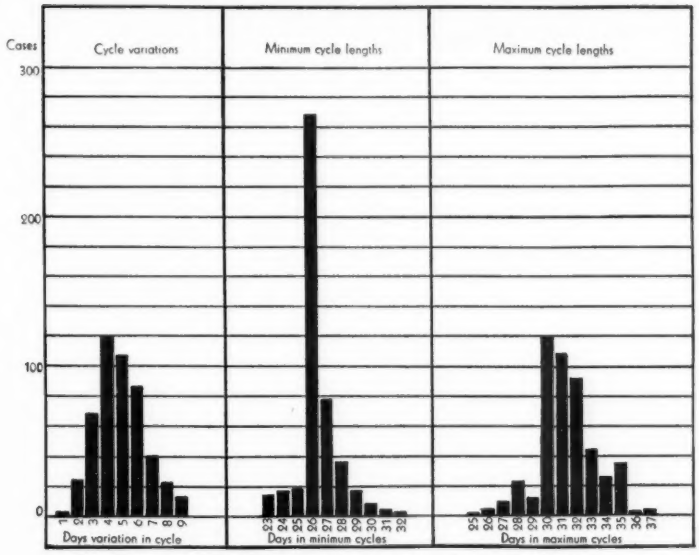


Fig. 4. Graphic presentation of Tables II, III, and IV.

period, although 7 of them used contraceptive methods. It is, of course, impossible for a doctor to enforce continence during the fertile period, but in all cases in which the patient's health had depended on the avoidance of pregnancy I have instructed them carefully and no failures have resulted.

During this study 27 women have used the fertile period procedure to space their pregnancies properly. In other words, they first avoided pregnancy and later conceived at the desired time through cohabitation during the fertile period. Fifteen women came seeking advice for the relief of sterility of one or more years' standing, and for the sole purpose of becoming pregnant. Six of them became pregnant after a single cohabitation during the fertile period. Two of the 6 afterward avoided conception for several months and then attained a second desired pregnancy through a single cohabitation during the fertile period. They are now using the procedure to avoid further conception.

RELIEF OF SUPPOSED STERILITY

The case of Mrs. G. H., age 32, married 8 years, is a good example of the relief of supposed sterility (Fig. 5).

She came to us complaining of sterility, but examination showed no essential reason why she could not become pregnant. Her menstruation record for 6 months revealed a 27 to 32 day cycle, the last menstruation date being July 26. During the month of August she cohabited just once, on August 13. No menstruation having occurred on August 30, a rabbit test for pregnancy was made and showed positive. In 280 days from the beginning of the last menstrual period she gave birth to a 9½ pound baby girl. Menstruation again occurred 4½ months after delivery and the menstrual record for the next

TABLE II.—CYCLE VARIATIONS OF 480 NORMAL WOMEN

Cycle variation in days	Number of cases	Per cent of cases	Cumulative percentage
1	2	.4	.4
2	24	5.0	5.4
3	68	14.2	19.6
4	120	25.0	44.6
5	106	22.2	66.8
6	85	17.7	84.5
7	40	8.3	92.8
8	22	4.5	97.3
9	13	2.7	100.0
	480	100.0	

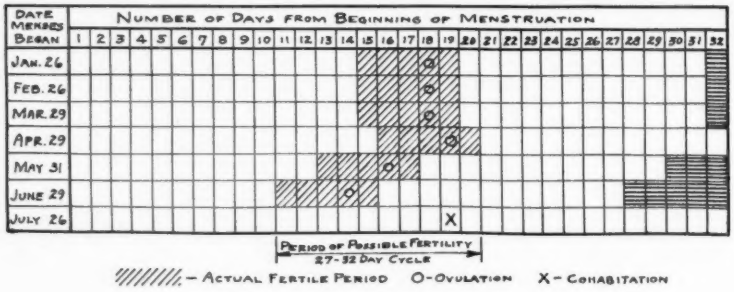

DATE MENSES BEGAN
NUMBER OF DAYS FROM BEGINNING OF MENSTRUATION
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32
JAN. 26
FEB. 26
MAR. 29
APR. 29
MAY 31
JUNE 29
JULY 26
PERIOD OF POSSIBLE FERTILITY
27-32 DAY CYCLE
- ACTUAL FERTILE PERIOD O-OVULATION X- COHABITATION

Fig. 5. Relief of supposed sterility.

6 months revealed a 28 to 32 day cycle. For the next 11 months she avoided pregnancy and, during the twelfth month, a single cohabitation during the fertile period resulted in a desired pregnancy. She gave birth to a 10 pound boy, 281 days after the beginning of the last menstruation. Four months later menstruation again commenced and a 6 month record showed a 28 to 31 day cycle. She is now using the fertile period procedure to avoid further conception.

A 5 YEAR COHABITATION RECORD

I am fortunate in being able to present the cohabitation record of Mrs. E. J., who has been noting the dates of her cohabitations and menstruations since 1931.

This woman first attempted to utilize the fertile period law after reading a lay book on the subject, and became pregnant twice. She was later instructed by me and has avoided pregnancy for several years. The cycle variation has been from 28 to 33 days and the location of the various cohabitations with respect to the period of possible fertility, the actual fertile periods and the ovulation dates, is shown in Figure 6. It is interesting to note that although the first day of the possible fertile period was violated in 5 instances during 1932 and 1933, no conception resulted.

TIME INTERVALS AMPLE AND PRACTICAL

That the time allotted for the life of the sperm cell and the fertility period of the egg cell is ample, there can be no doubt, because many women have reported violations of the first and last days of the period of possible fertility. Still no pregnancy resulted and a careful examination of their records show that they missed the actual fertile period for the current cycle by only one day. A case in point is reported in brief as follows:

TABLE III.—MINIMUM CYCLE LENGTHS OF 480 NORMAL WOMEN

Minimum cycle in days	Number of cases	Per cent of cases	
23	14	2.8	
24	16	3.3	
25	18	3.7	
26	269	56.1	
27	77	16.1	83.9
28	56	11.7	
29	17	3.5	
30	8	1.7	
31	3	.6	
32	2	.5	
	480	100.0	

TABLE IV.—MAXIMUM CYCLE LENGTHS OF 480 NORMAL WOMEN

Maximum cycle in days	Number of cases	Per cent of cases	
25	1	.2	
26	4	.8	
27	9	1.9	
28	23	4.8	
29	12	2.5	
30	119	24.8	
31	111	23.1	76.1
32	91	19.0	
33	44	9.2	
34	25	5.2	
35	35	7.3	
36	2	.4	
37	4	.8	
	480	100.0	

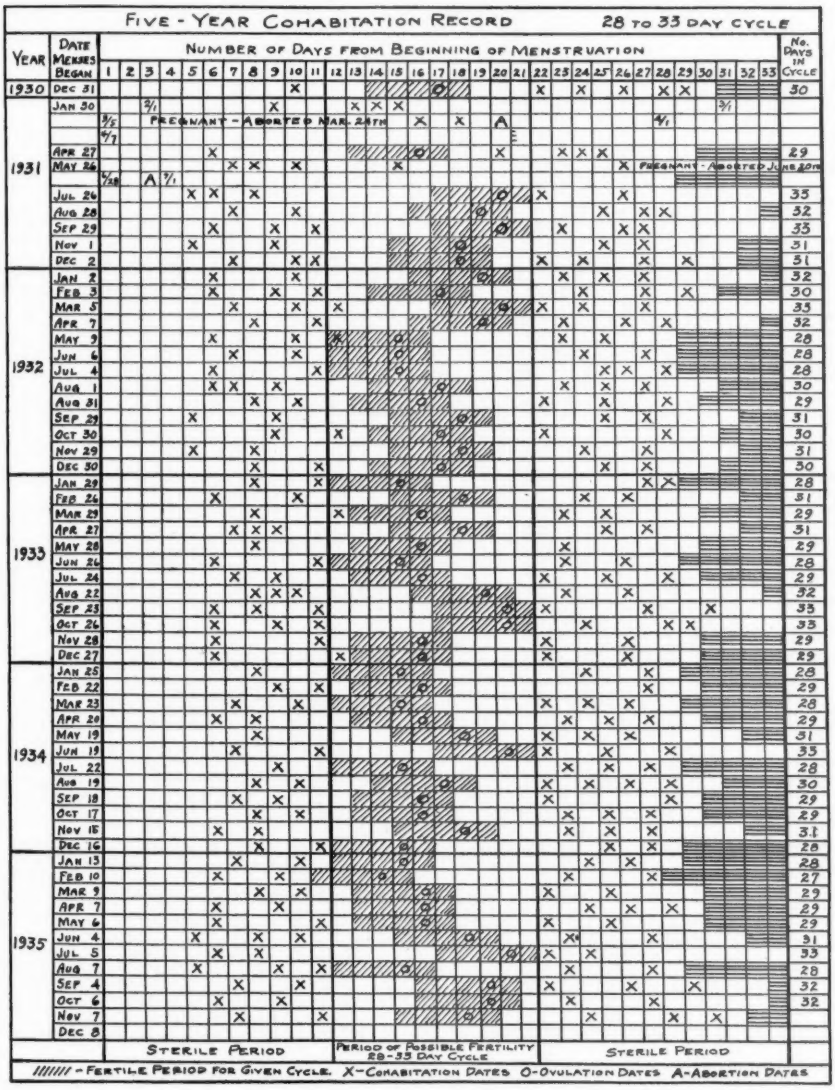


Fig. 6. Five year cohabitation record.

Mrs. F. G., aged 35 years, married at the age of 20, had 3 children, the youngest aged 10 and an incurable idiot. Because of the great burden her youngest child has been to her family she did not desire more children for fear that they too might be feeble minded. In spite of the fact that she earnestly sought contraceptive advice and had used various types of vaginal suppositories, jellies, and cones; also a combination of jellies and rubber diaphragms; a gold stem pessary; also lemon juice, lysol, potassium permanganate, boiled milk and iodine as douches; nevertheless, during the following years she became pregnant six times and underwent six self-induced abortions. Having heard of the fertile period theory she came with an 8 months' record of her menstruation dates and volunteered the infor-

mation that her cycle was exactly 26 days. A careful check showed it to have a 24 to 26 day variation. A suitable calendar was furnished to her with specific instruction for its use. A year later she returned with the calendar properly marked to show menstruation dates and cohabitations. This time she informed me that the device had certainly been a God-send to her, that she had had 66 cohabitations and had not become pregnant. Careful study of the calendar revealed some startling facts which, nevertheless, show that there is a considerable safety factor in the time intervals used. She had coitus five times on the first day of the possible fertile period, five times on the last day of the possible fertile period, and three times she violated both the first and last days of the same period. Still no pregnancy resulted because she missed the actual fertile period by exactly one day in each instance.

TEDIOUS CALCULATIONS ELIMINATED

For most doctors and their patients calculations of the various periods are tedious and subject to error. Fortunately, accurate charts have been published giving the required information instantly when the cycle has been determined from the patient's written record.

In my practice I use a chart which shows the fertile periods, the sterile periods, and the time of ovulation for about 90 different cycle variations. It also indicates, by means of an accessory aid, the actual calendar dates in any period and the number of days between any two consecutive menstruation dates. This chart is very much worth while, because it obviates counting on the calendar, saves time, and eliminates the chance of error.

TIME INDICATORS FOR PATIENT'S USE

The last necessity for the doctor who utilizes the fertile period procedure for his patients is a means for getting the information to them in some usable form which will eliminate as far as possible the chances of error on their part. There are available a variety of indicating devices and many lay books have been published on the subject. The lay books are all very interesting to read, but our experience has been that most women are not able to apply the published information in a practical manner, their calculations being about 90 per cent wrong.

During this 5 year study 7 different styles of indicating devices or individual calendars have been investigated. Although elaborately constructed, one was applicable only to women with a cycle variation of 26 to 31 days. Three others were discarded as being much too complicated, even for most physicians. A fifth one was found to locate ovulation 15 days before the following menstruation, and investigation showed that 5 pregnancies had resulted from coitus on the first indicated non-fertile day after ovulation. A sixth was found to be thoroughly reliable, but indicated what seemed to us an unusually long fertile period. The seventh is now being generally used by our patients. It is made up to suit any one cycle variation only, incorporates a standard continuous calendar, and is therefore less liable to error. Unlike all others, it is distributed only through the medical profession. During the past 3 years it has had no recorded failures in more than 30,000 cohabitations.

PRACTICAL AND SIMPLE ROUTINE PROCEDURE

Beyond these indicating devices the doctor needs no further equipment to put the fertile period procedure into practice. In this clinic every menstruating woman is told of the importance of an accurate menstrual record and is given a suitable card on which to record the dates. Every recently confined woman is instructed as to the importance of spacing pregnancies. A regular, completely effective routine has been developed, in which there are only four comparatively simple steps:

1. Get from the patient a list, written down at the time, of the last 6 or 8 menstruation dates.
2. Determine the cycle variation from the longest and shortest cycles in the list.
3. Examine the patient for abnormal pelvic conditions and correct those found, if necessary.
4. Furnish to the patient an indicator or individual calendar that is as nearly fool-proof as possible.

SUMMARY AND CONCLUSIONS

A 5 year clinical study of the fertile and sterile periods of women has been made. This study quite definitely points out the value of accurate menstrual records as an early diag-

nostic aid of abnormal female sex organ function. It also shows that ovulation has a definite time relationship to the next succeeding menstruation, and indicates that the time between ovulation and the next menstruation is a matter of 14 days.

1. The regularity, duration, and character of the menstrual periods are the chief signs indicating normal or abnormal female sex organ function.

2. Barring accident or disease the menstrual cycle of a normal woman varies continually between a certain maximum and minimum number of days.

3. Ovulation has a definite time relationship to the next succeeding menstruation and, regardless of the rhythm in the menstrual cycle, this relationship does not change.

4. That there are definite periods of physiological fertility and sterility in the menstrual cycles of normal women appears to be a definitely established biological law.

5. The fundamental scientific basis of the fertile period procedure is sound and reliable. The procedure offers to mankind, when it is supervised by a physician, a simple, dependable, and physiological method for conception control.

METHODS OF DEMONSTRATING THE ACTIVITY OF CORPUS LUTEUM

DAVID I. MACHT, M.D., F.A.C.P., Baltimore, Maryland

THE exact number of ovarian hormones present in the body of higher animals is still in dispute. Many think there are at least three such internal secretions—the follicular hormone, the corpus luteum hormone, and the hormone of interstitial tissue; others, a larger number. Fraenkel's early researches stressed corpus luteum as the most important internal secretion of the ovary, a view which prevailed for some years although slightly modified by Marshall and others. Later, studies on the effect of x-rays on the female gonads brought the function of the so called interstitial ovarian tissue into prominence and pointed to the endocrinological action of that tissue, elucidated by the work of Bouin, Ancel and Villemin, and of Steinach and Holzknecht. Following the interesting researches of Stockard and Papanicolaou (93) concerning the histological changes in the gonads and accessory organs produced at various periods of the estrus cycle, an enormous amount of work was done on the cellular structure of the vaginal epithelium which culminated in the study of the estrogenic or follicular hormone by means of vaginal smears. These researches, popularized by the writings of Allen and Doisy (3), S. Loewe, and others, directed the attention of physiologists to the function of the follicular fluid and stressed the hormones contained therein as the principal endocrine product of the ovary. While the exact number of ovarian hormones is still unsettled and their chemical nature occasions even more dispute among those investigators who have been working on the biochemistry of the gonads, it is the general consensus that the female gonad elaborates at least two different hormones quite distinct in their physiological function. One of these is the follicular hormone, often known by other names such as estrogen, folliculin, amniotin, menformon, etc.; the other is an internal secretion elaborated by corpus luteum, particularly when fully developed. The physiological action of the follicular hormone can be demonstrated in several ways and especially by the study of the vaginal epithelium obtained from smears or scrapings of castrated female rats, mice, and guinea pigs. The character of the cells thus obtained changes after such castrated animals have been injected with estrogenic hormone. Demonstration of the physiological function of corpus luteum, although effected in any one of a number of ways, is much more difficult. The purpose of the writer is to offer a brief résumé of the physiological procedures employed for detecting and demonstrating the activity of corpus luteum either *in vivo* or by pharmacological use of corpus luteum extracts, and furthermore to describe and present his experiences with some of the newer methods of approach more recently employed in that connection.

Experimental data pointing to physiological action of corpus luteum hormones may be classified as those pertaining to (1) the relation of corpus luteum to pregnancy; (2) the relation of corpus luteum to menstrual cycle of monkeys and human beings; (3) histological changes produced by corpus luteum in sexual apparatus; (4) changes effected by corpus luteum in vaginal epithelium; (5) gross anatomical changes produced by corpus luteum hormone in uterus, etc.; (6) influence of corpus luteum on contractions of smooth muscle; and (7) miscellaneous physiological effects produced by corpus luteum.

1. RELATION OF CORPUS LUTEUM TO PREGNANCY

Pearl and Surface have described an inhibition of ovulation following intraperitoneal administration of a fat-free preparation of corpus luteum substance. Haberlandt, Knaus (47) and Kennedy noted that temporary sterility of females was produced by injections of corpus luteum extracts. On the other hand, Loeb, and Corner and Hurni (14) in their ear-

lier papers on the subject reported that corpus luteum extracts failed to inhibit ovulation in rodents. The present view universally held by all students of the subject, however, is that corpus luteum is directly concerned with the course of pregnancy. Corner (12) sums up the matter in this way: Broadly speaking, the endocrine function of the corpus luteum is a part of the mechanism of pregnancy. Its action is exerted on the uterus to prepare that organ for the reception and nutriment of the embryo. When the ovum begins its journey through the fallopian tubes, the follicle whence it took its origin gives place to the corpus luteum, and this newly formed corpus luteum begins to deliver into the blood stream a substance causing extensive development of the uterine glands and changing the histological structure of the uterine mucosa or endometrium. By the time the fertilized ovum reaches the uterus, the endometrium through this action upon it of corpus luteum hormone is in a state of heightened secretory activity by which nutritive substances are provided for the embryo. Furthermore, through the action of the corpus luteum secretion, the endometrium is sensitized so that it responds to the presence of the embryo by forming the maternal part of the placenta. It has been shown experimentally that removal of corpus luteum from an animal during the early part of pregnancy results in failure to implant the embryo or, if the embryo is already implanted, effects a deterioration of the pregnancy. Corner found that injection of corpus luteum extract in castrated rabbits produced pregnancy changes in the uterus. In rabbits castrated during early pregnancy, injection of progestin protected the embryos against the loss of their mothers' corpora lutea and maintained the pregnancy to full term. In guinea pigs progestin was found to sensitize the uterus to produce the maternal placenta or so called Loeb's *deciduoma*.

2. RELATION OF CORPUS LUTEUM TO MENSTRUATION

It is now generally known that menstruation is not identical with ovulation although it bears a definite relation to the estrus cycle of various animals, including human beings. Physiologically speaking, menstruation is the last effort made in the sex cycle of higher animals after there has been failure to conceive. It has been shown in women (100) and in monkeys (80) that menstruation, disappearing as a result of ovariectomy, may be induced experimentally by treatment with estrogenic substances. On the other hand, Pratt claims that excision of corpora lutea in adult primates will precipitate menstruation. It has been demonstrated that the injections of corpus luteum extract may delay or postpone menstrual periods experimentally produced in monkeys. It is now generally agreed that, in the normal menstrual cycle, both the estrogenic or follicular hormone and corpus luteum play rôles. Typical progestatized endometrium has been produced in ovariectomized monkeys by successive folliculin and corpus luteum injections (35). Similar experiments have been reported by Smith and Engle (89), and Kaufmann has actually produced premenstrual endometrium in castrated women by first administering large doses of estrogenic substance to bring the uterus back to its normal interval stage and then injecting corpus luteum extract to effect the premenstrual changes. A proper balance between the follicular and corpus luteum hormones is essential for normal menstruation, as estrogenic substance has been demonstrated in the human corpus luteum during the premenstrual stage (2, 4). These studies on menstruation point unequivocally to an important endocrinological function of the corpus luteum in primates but the methods employed are too complicated for practical routine assay of the hormone.

3. HISTOLOGICAL CHANGES INDUCED BY CORPUS LUTEUM EXTRACTS

Various investigators have found that progestin or corpus luteum hormone produces histological changes in different lower animals and also in human beings. Corner states that administration of progestin produces pregnancy changes in uterus of castrated rabbits. Corpus luteum extracts, administered to rabbits castrated during early pregnancy, as has already been stated, protect the embryos against loss of the mothers' corpora lutea and

induce characteristic pregnancy changes in the uterus, and corpus luteum hormone, administered to guinea pigs, sensitizes the uterus and produces the maternal placenta or so called Loeb's *deciduoma*. Later work by Hisaw, Meyer and Fevold, by Smith and Engle, and by Corner revealed that progestin, administered to monkeys, produces a picture characteristic of premenstrual endometrium. So characteristic is the change produced by progestin in rabbits, according to Corner and Allen (13), that they have advocated as a standard for assaying it the so called *rabbit unit*, which is the amount of the hormone (divided into 5 equal daily doses) that will produce on the sixth day a microscopic condition of the uterus equal to that of the eighth day of normal pregnancy. Injections of corpus luteum hormone have also produced physiological changes in other and more remote organs.

Herrmann and Stein (32) reported that when injected in young male rats and rabbits, the estrogenic hormone delayed attainment of sexual maturity and furthermore that large quantities of corpus luteum hormone, injected in adult rats and rabbits, produced in the testes degenerative changes not unlike those produced by x-rays. Fellner (20, 21) repeated and extended this work and discovered that degeneration of testes was produced by injections of placental or corpus luteum lipoids. This so called "antimasculine" property of corpus luteum is of interest in connection with the peculiar reaction of the vas deferens and seminal vesicles described by Macht and Matsumoto. The latest study on histological changes is that made by Pincus and Werthessen, who have correlated the activity of corpus luteum preparations with microscopic measurements of the actual size of the ovum. All such studies as those mentioned, however, require very complicated technique and are not suitable for practical bioassay of corpus luteum preparations. One special method of histological character, however, is adapted to the assay of estrogenic substances and has been employed by the present writer also in testing corpus luteum extracts and preparations. It is the study of the vaginal epithelium.

4. EFFECT OF CORPUS LUTEUM HORMONE ON VAGINAL EPITHELIUM

The most popular method for studying female hormones, derived from the follicles and spoken of as the follicular or estrogenic hormones or theelin, may be described as follows: Vaginal smears obtained from normal intact rats or mice present periodic variations in the number and character of epithelial, blood, and other cells in relation to their estrus cycles. In castrated or ovariectomized animals a typical and constant picture of the diestrual stage is maintained. When injections of estrogenic hormone are given to such animals, however, the character of the vaginal cells changes and repeated injections produce a picture of estrus. Accordingly, use has been made of such changes in vaginal cells in assaying preparations of that type.

Can any change in character of the cells obtained from vaginal smears be effected by administration of corpus luteum hormone? Corpus luteum, in contrast to estrogenic substance, can obviously not be expected to stimulate estrus. On the other hand, there is a possibility of its acting synergistically or antagonistically to follicular hormone. A number of investigators have attacked this problem. The most satisfactory experiments with corpus luteum on the estrus cycle of animals were obtained not with mice or rats (because of the short duration of their cycles) but with guinea pigs, the estrus cycle of which is considerably longer (10 to 12 days). Thus, Papanicolaou, who injected extracts from the corpus luteum in guinea pigs, reported inhibition of estrus, determined by the smear method over extended periods, while negative results were obtained in control tests on follicular fluid, placenta, and other tissue. Papanicolaou considers this the proper luteal hormone. Parkes and Bellerby obtained vaginal reactions in mice by injecting small doses of follicular fluid after ovariectomy and attributed such results to removal of corpus luteum inhibition. Voss has also effected an inhibition in guinea pigs by administering corpus luteum extracts.

The present writer in collaboration with Stickels and Seckinger (65) has for several years carried on studies along these lines,

the results of which indicate that such corpus luteum injections, as compared with those of the follicular hormone, exert an antagonistic action. The experiments were made on various series of guinea pigs. For a long time the normal cycle of each animal was determined by vaginal smears. After the duration of the respective animals' estrus cycles had been established, guinea pigs were given repeated daily injections of water-soluble corpus luteum extracts (prepared by various methods); and their effect on the duration of the cycle was observed. It was found that the corpus luteum injections markedly prolonged the *diestrus* or interestrual interval. Table I reveals the findings obtained in experiments with 27 such animals. While the average diestrus of normal or untreated animals was 11.9 days, that of the guinea pigs thus treated with corpus luteum extracts was 44.7 days. These figures demonstrate decisively that corpus luteum greatly prolonged the interestrus interval. Of further interest was a supplementary study made by Macht and Stickels (62) in which corpus luteum was not injected but fed to guinea pigs for long periods. Table II shows the results obtained in these tests.

TABLE I.—EFFECT OF INJECTIONS OF CORPUS LUTEUM ON ESTRUS CYCLE OF THE GUINEA PIG

Guinea pig number	Days of normal interestrus	Days of interestrus after injections of corpus luteum
1	13	29
2	12	25
3	12	22
4	12	64
5	14	48
6	13	59
7	12	42
8	13	30
9	13	30
10	13	46
11	14	14
12	13	39
13	12	47
14	14	29
15	10	30
16	9	22
17	9	30
18	15	33
19	9	20
20	9	22
21	9	22
22	10	23
23	15	30
24	9	22
25	15	41
26	11	33
27	12	36
Average	11.9	44.7

5. CHANGES IN GROSS ANATOMY

Besides the histological or microscopic changes produced by female sex hormones injected under specified conditions, marked changes in the *gross* appearance of various organs have also been observed after such treatment. Indeed, the most important criterion of the activity of extracts used in earlier work on this subject was the gross appearance of the uterus and gonads. Many such changes were noted after injection of follicular extracts in one form or other. The aim of some of the early injection experiments was to "maintain uterine nutrition," inasmuch as removal of both ovaries was invariably followed by atrophy of the uterus. Such administration of some of the extracts was followed by most striking results (1, 11, 22, 24, 31, 38, 39, 71, 83, 84, 85). Another criterion was the *swelling* and *hyperemia* produced by ovarian extracts in area surrounding the external genitalia of rabbits, pigs, dogs, and monkeys (91). Changes in size of the uterus in the smaller rodents were of special interest. Zondek and Aschheim (102) noted an increase in size of uterus of mice injected with follicular extracts. Similar observations were made by Kochmann. Other changes were noted in the mammary glands (7, 55) of both males and females but especially of the latter. Frank and Rosenbloom noted that certain ovarian extracts injected in rabbits stimulated the growth of not only the uterus but also the vagina, breasts, and accessory organs, while Courrier observed that they accelerated development of the uterus and other genitalia in newly born animals. After continued treatment of rats with

TABLE II.—EFFECT OF PROLONGED FEEDING OF CORPUS LUTEUM, ETC., ON ESTRUS CYCLE

Animal number	Normal diestrus, days	Animal fed	Time animal was maintained on specified diet, weeks	Resultant diestrus, days
1	7	No ovary	4	8
2	9	No ovary	4	9
3	8	No ovary	4	9
4	10	No ovary	4	10
5	12	No ovary	4	11
6	8	Lutein	4	10
7	6	Lutein	4	11
8	8	Lutein	4	8
9	10	Lutein	5	15
10	7	Lutein	5	10
11	14	Lutein	5	14
12	11	Lutein	5	11
13	9	Lutein	5	12
14	6	Lutein	6	12
15	8	Lutein	6	12
16	8	Lutein	6	12
17	9	Lutein	6	13
18	2	Lutein	6	8
19	6	Lutein	6 and 8	15–20
20	9	Lutein	6 and 8	16–35
21	8	Lutein	6 and 8	16–18
22	8	Lutein	6 and 8	19–22
23	8	Lutein	6 and 8	16–19
24	8	Folliculin, C	4	3
25	9	Folliculin, A	4	5.5
26	8	Folliculin, D	4	4.5
27	8	Folliculin, B	4	2
28	9	Folliculin, F	4	6
29	12	Folliculin, F	4	4
30	13	Folliculin, E	4	14
31	10	Folliculin, E	4	10
32	8	Folliculin, F	4	3

anterior lobe of the pituitary, Long and Evans found that the ovaries were enlarged as the result of formation of many corpora lutea.

Have any gross anatomical changes been noted after administration of corpus luteum? As late as 1927 Allen and Doisy stated that they knew of "no successful attempts to inhibit the action of injected follicular hormone by injection of corpus luteum extract." More recently, the present writer, collaborating with Stickels, has obtained some interesting results in studies on synergistic effects of combinations of estrogen and corpus luteum hormones. This work was stimulated by the interesting finding of Siddall, who developed a novel test for pregnancy. It was found that the usual ratio of the uterus weight of a mature non-pregnant white mouse to its body weight is over 1:400. Normal mature mice were injected with follicular estrogenic extracts for 7 to 10 days, at the end of which period they were killed and the weight of the uteri determined. Such injections markedly increased the size of the uteri so that the ratio of its weight to that of the body fell far below 1:400.

Macht and Stickels (63) undertook similar studies with both the estrogenic hormone of the ovary and with corpus luteum extracts. A series of mice, injected daily for 2 weeks with a standard estrogenic extract, were then killed; and the ratio of the uterus weight to that of the whole body was determined. A marked hypertrophy, shown by increase in the weight of the uteri, was noted. In a second series, mice injected with corpus luteum extract alone revealed no change in size or weight of the uterus. A third series of mice was injected for the same length of time with a mixture of the same estrogenic preparation and a water soluble corpus luteum extract prepared in this laboratory. The most striking discovery made was that *no hypertrophy*, such as had succeeded injection of estrogenic extract alone, *followed administration of a combination of estrogenic and corpus luteum extracts*. These experiments clearly revealed that lutein antagonized or inhibited the stimulating action of the follicular hormone. Table III strikingly illustrates these findings. This antagonism between corpus luteum and follicular extracts was noted not only in injection experiments but also after feeding experiments, prolonged for several weeks, in which the two hormones were administered, in combination, to mice. The findings in these experiments are shown in Table IV.

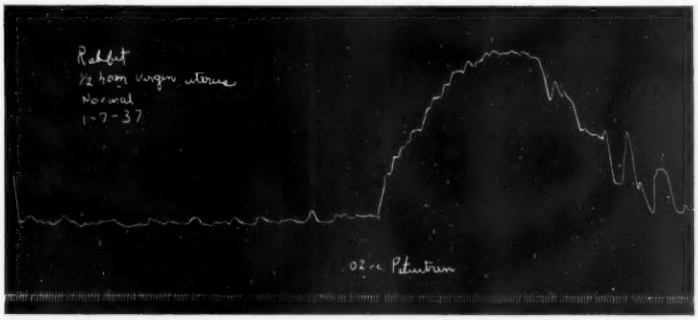


Fig. 1. Stimulation of uterus of virgin rabbit effected by 0.02 cubic centimeter of pituitrin (surgical, P.D.).

6. RELATION OF FEMALE GONADS TO ACTIVITY OF UTERINE AND OTHER SMOOTH MUSCLE ORGANS

A. *Relation to posterior pituitary hormone.* In recent years studies on the contractions and tonicity of the smooth muscle from the uterus, fallopian tubes, seminal vesicles, vasa deferentia, etc., have thrown considerable light on the intricate physiology of the sex hormones and yielded useful criteria for evaluating their activity, particularly that of the corpus luteum. Knaus (48, 49, 50) established the fact that the excised uterus of a rabbit under the influence of a functioning corpus luteum did not respond to treatment with the posterior pituitary hormone *in vitro* as did the virgin uterus, whereas even minute doses of pituitrin effected a powerful contraction in the control, taken from a virgin rabbit.

While it is generally accepted that the estrogenic hormone stimulates the contractions of the uterus, as shown by the work of Parkes, Kelly, Zondek and Aschheim (103), Brouha, and others, accumulated evidence reveals that in normal higher animals and the human being, the corpus luteum hormone inhibits or quiets contractions of the uterus. Thus Knaus (51) and Manzi maintain that the uterus is kept in a state of quiescence during pregnancy by the influence of the corpus luteum and when, toward the end of pregnancy that effect diminishes, the organ becomes more

TABLE III.—EFFECT OF INJECTIONS OF ESTRIN ALONE AND ESTRIN PLUS LUTEIN ON WEIGHT OF MOUSE UTERUS

Mouse number	Estrin alone, 0.2 c.cm. daily			Estrin, 0.2 c.cm., plus lutein, 0.5 c.cm., daily		
	Weight of body in milligrams	Weight of uterus in milligrams	Ratio of uterus to body weight	Weight of body in milligrams	Weight of uterus in milligrams	Ratio of uterus to body weight
1	20,000	50	400	22,700	25	908
2	22,200	50	444	19,500	20	975
3	25,800	65	397	24,700	45	549
4	27,200	70	389	19,000	20	950
5	22,000	170	129	27,200	85	320
6	20,150	55	366	16,800	30	560
7	20,840	55	379	21,450	30	715
8	20,550	55	374	20,950	30	698
9	25,560	125	204	23,400	45	520
10	22,500	110	205	21,550	50	539
	Average		282	Average		587

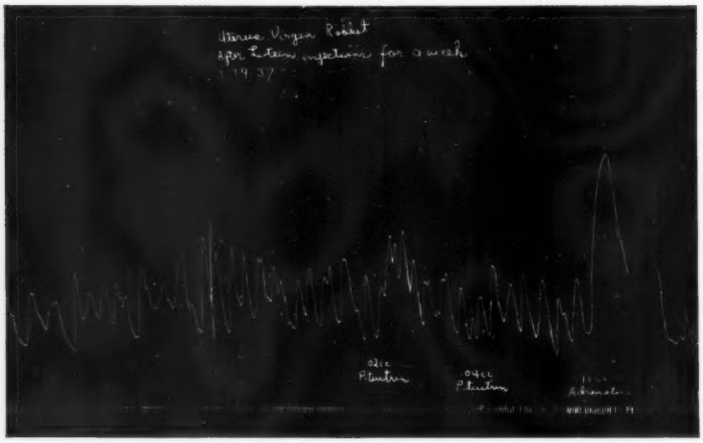


Fig. 2. Effect of repeated injections of lutein (H.W.&D.), totaling 30 cubic centimeters, on uterus of virgin rabbit.

sensitive to the influence of the posterior lobe of the pituitary. The work of the Smiths (90) indicates that during pregnancy a physiological balance is maintained between estrogenic and corpus luteum hormones. As pregnancy progresses, the estrogenic principle, becoming more dominant, sensitizes the uterus to the oxytocic influence of the posterior lobe of the pituitary, and thus labor follows. Allan and Dodds (5) expanded this theory of labor onset. Inasmuch as corpus luteum vitally affects the normal course of pregnancy, on the one hand, and inhibits the motility of the uterus, on the other, numerous investigators have successfully employed extracts of corpus luteum to prevent abortion and maintain the normal course of pregnancy. Miklos prolonged pregnancy in rats with aqueous extracts of corpus luteum. Clinically, Hirst injected aqueous extracts of corpus luteum from pregnant cats to prevent habitual abortion. Hofbauer reported that in threatened

TABLE IV.—EFFECT OF ESTRIN AND ESTRIN PLUS LUTEIN FEEDING ON WEIGHT OF MOUSE UTERUS

Mouse number	Estrin alone, 2 to 5 mouse units daily			Estrin, 2 to 5 mouse units, plus 0.5 c.cm. of lutein solution, daily		
	Weight of body in milligrams	Weight of uterus in milligrams	Ratio of uterus to body weight	Weight of body in milligrams	Weight of uterus in milligrams	Ratio of uterus to body weight
1	21,600	55	393	21,840	30	728
2	27,000	70	357	24,440	40	611
3	28,000	80	350	21,000	25	840
4	28,100	80	352	18,370	22	835
5	23,600	60	393	17,820	20	891
6	24,700	65	380	20,370	25	815
7	27,150	70	388	24,620	40	616
8	20,520	55	380	13,580	19	714
9	13,940	35	398	15,900	20	795
10				22,500	35	898
	Average.....377			Average.....774		

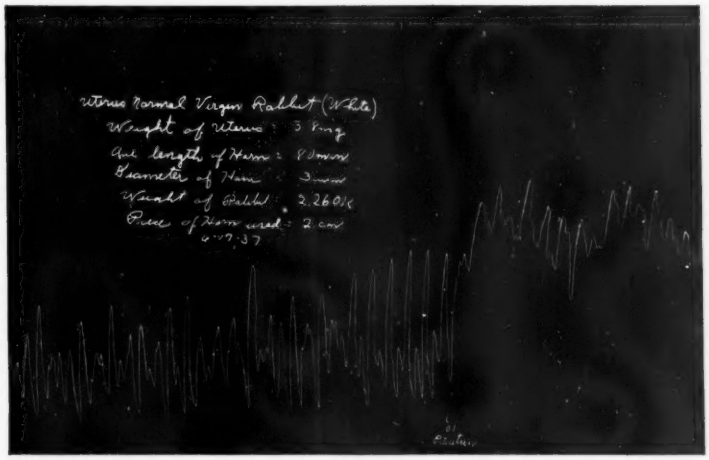

Uterus Normal Virgin Rabbit (White)
Weight of Uterus: 3 mg
Total length of Horn: 8 cm
Diameter of Horn: 3 mm
Weight of Rabbit: 2.260 K
Piece of Horn used: 2 cm

Fig. 3. Effect of 0.01 cubic centimeter of pituitrin (surgical, P.D.) on uterus of normal virgin rabbit.

and recurrent abortion uterine contractions were inhibited by such an extract. Halban advocated the employment of corpus luteum in the treatment of abortion, and the successful use of such preparations has been reported by Glismann, Antecki and Zwolinski, Wolfson, Weinzierl, Bracht, Wagner, and Knab. Krohn, Falls and Lachner employed corpus luteum for the treatment of threatened and habitual abortion and have recently (by a balloon method) demonstrated that corpus luteum inhibited the contractions of the uterus (19). More recently, Robson and Illingworth, and de Fremery, Luchs, and Tausk have studied various fractions obtained from corpus luteum extracts and found that one of these, which they called "desensin," thus inhibits the action of pituitrin on the uterus. Similar findings were made by Foster, and especially by Reynolds. Corner (66) and his associates used such uterine preparations in assaying a corpus luteum hormone which they prepared and named "progestin."

The present writer has been experimenting on rabbits for over a year in order to study these remarkable variations in contractions of uterine muscle in relation to the influence of corpus luteum hormone and that of the posterior lobe of the pituitary gland. In these studies the writer employed an aqueous solution of the corpus luteum (prepared in these laboratories) of which numerous physicians have made wide clinical use with allegedly favorable therapeutic results. Healthy normal virgin rabbits were selected. In some, ovariectomy was performed; in others, the ovaries were left intact. A standard preparation of pituitrin (P.D.) was used for testing the oxytocic response of uterine muscle. In most of the experiments one horn of the virgin uterus was removed under aseptic conditions and the animal was allowed to recover. The contractions with which the excised tissue in oxygenated Locke solution responded to small doses of pituitrin were carefully recorded. The rabbit operated upon was then given repeated intravenous injections of corpus luteum extract for 10 days, after which the other horn of the uterus was studied in similar fashion. It was found that injections of lutein (H.W.& D.) effected in behavior of the muscle such a change as that described by Corner and other previous writers. Uterine preparations (from mature rabbits) previously treated with lutein gave a much weaker response to pituitrin and, after very large doses of lutein, did not react to pituitrin at all although other oxytocic agents effected a contraction of the muscle. The subjoined curves show the type of response obtained in control animals, on

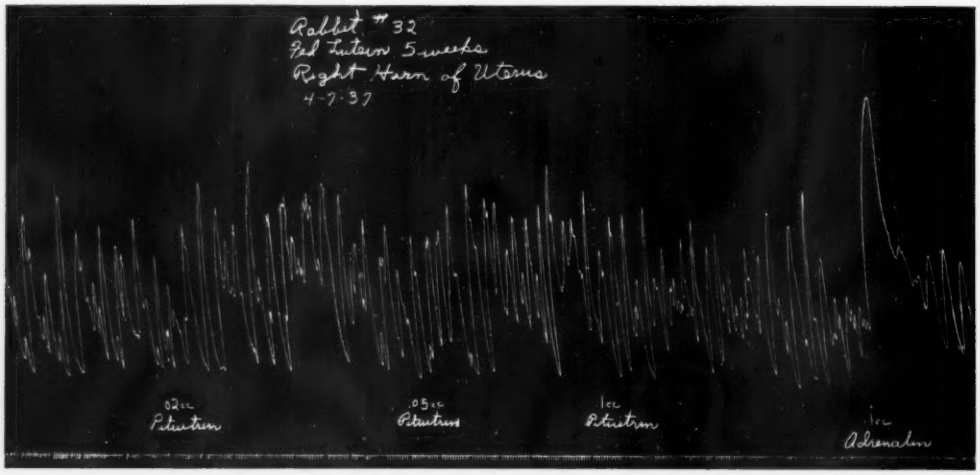


Fig. 4. Small effect produced by the administration of pituitrin (surgical, P.D.) on horn of uterus of virgin rabbit which had been fed desiccated lutein (1 gm. a day) for a period of 5 weeks.

the one hand, and in rabbits treated with corpus luteum extract, on the other (Figs. 1 and 2). A comparison of the writer's curves with those of other investigators revealed that a cubic centimeter of the corpus luteum solution exerted an action similar to that effected by 0.1 milligram of progesterone.

Although, generally speaking, considerable skepticism exists regarding the effectiveness of the female sex hormone products administered *per os*, the writer is inclined to believe that the feeding of such preparations, when continued for a sufficient length of time, does have a definite physiological action. The writer has performed experiments in which, instead of injecting extracts of corpus luteum, the desiccated gland was *fed* by stomach to rabbits for several weeks. In control experiments other rabbits were given the same food minus the powdered corpus luteum. The corpus luteum powder used in these experiments was prepared from fresh glands desiccated at low temperature. Figures 3 and 4 illustrate the results obtained with uterine muscle preparations from controls and from rabbits fed with such powder. It was found that just as injections of corpus luteum weakened the response of the muscle preparation to subsequent treatment with pituitrin or completely suppressed it, so the continued feeding of desiccated corpus luteum rendered responses of uterine muscle from rabbits very feeble. The difference between the results obtained in the injection and feeding experiments were quantitative rather than qualitative. Of course, the feeding experiments had to be continued for a considerably longer time before the physiological effect mentioned could be obtained.

B. Relation to epinephrin. Of great physiological interest as well as of practical value is another remarkable phenomenon noted recently in studies on the rhythmic contractions of uterine muscle, i.e., the response of such muscle to epinephrin in relation to the influence of female sex hormones. It has been known for a long time that the uterus of the virgin cat responds differently to stimulation of the hypogastric nerves *in vivo* or to treatment with epinephrin both *in vivo* and *in vitro* from that of the animal in pregnancy. The normal virgin uterus of the cat is relaxed by epinephrin but the uterus of the pregnant cat *in vitro* contracts when treated with the same drug. This remarkable reversal of the usual response of the cat's uterus to epinephrin suggested to Van Dyke and Gustafson that the explanation of the phenomenon might lie in an

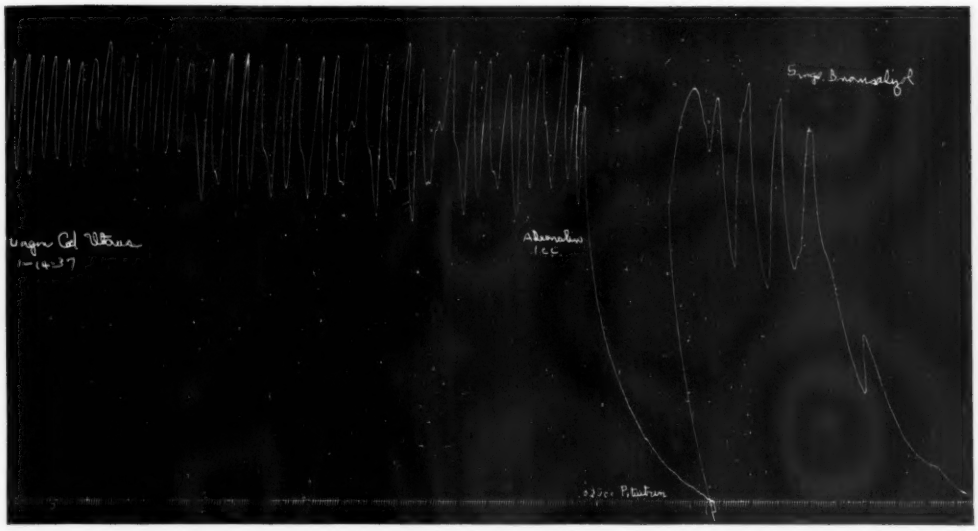


Fig. 5. Relaxation of uterus of virgin cat effected by injection of 0.1 cubic centimeter of a 1:1000 solution of adrenalin, followed by stimulation produced by 0.025 cubic centimeter of pituitrin (surgical, P.D.) and, finally, by relaxation on addition of 5 milligrams of bromsalizol.

alteration of character of the sex hormone set free in the cat's circulation during pregnancy. Accordingly, those authors, experimenting with injections of progestin or corpus luteum extract in cats, found that a reversal of epinephrin action took place in virgin cats under such conditions. Similar experiments were made by Kennard, and recently on guinea pigs by Holtz. The present writer, desiring to duplicate the experiments made by the American investigators, carried out a series of such studies on virgin and pregnant animals. The results obtained fully agreed with those described. It was found that uterine preparations obtained from normal virgin cats and studied *in vitro* responded to adrenalin with relaxation of the tonus and inhibition of contractions. On the other hand, it was found that the uteri of virgin cats, injected intravenously for 2 weeks daily with extracts of corpus luteum, reacted paradoxically when treated with adrenalin and responded with much less relaxation and sometimes none at all although a positive pressor effect or contraction was noted rarely. The subjoined curves illustrate these findings (Figs. 5, 6, and 7).

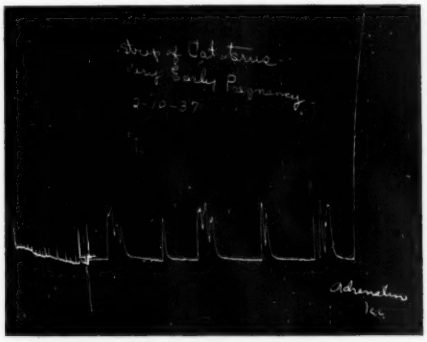


Fig. 6. Stimulation adrenalin produces in uterus of cat in early pregnancy (1 to 2 weeks).

C. Physiological responses of the vas deferens. Some years ago Macht and Matsumoto described a third phenomenon in regard to the contractility of smooth muscle organs in relation to the sex hormones. Those findings have more significance at the present time than they conveyed 18 years ago. The authors undertook a study of the physiological effects of all kinds of glandular extracts on the motility of the genito-urinary organs or, more specifically, on the contractions of the smooth muscle they contain. The effects of various

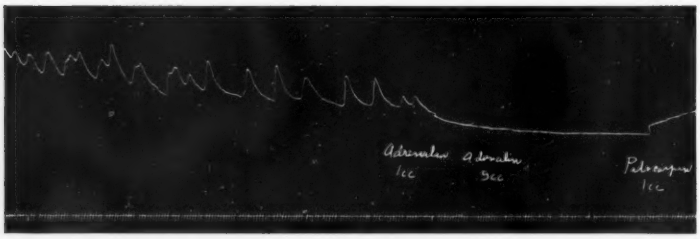


Fig. 7. Effect of adrenalin on uterus of virgin cat, which had been daily injected intraperitoneally with lutein (H.W.& D.) for 8 days, the total amount injected being 28 cubic centimeters. Note inhibition of contractions but no relaxation of muscle.

glandular extracts on the uterus, fallopian tubes, seminal vesicles, vas deferens, bladder, and ureters of various kinds of animals were carefully studied.

It was found that while aqueous or saline extracts of all sorts of glands (with the exception of the suprarenal) effected but a mild stimulation of smooth muscle preparations, corpus luteum extracts produced an extraordinary stimulation of vasa deferentia of rodents, particularly of white rats. Even minute quantities of such corpus luteum extracts produced powerful contractions of the vas which, within biological limits, were proportional to the amount of the extracts used.

Extracts of whole ovary also stimulated the vas deferens of the rat to some extent but it was demonstrated that such contraction was effected by the corpus luteum present in the preparations. When ovarian or follicular extracts free from corpus luteum were examined in this way, the response was very weak. These observations of Macht and Matsumoto (69) suggested a simple and ready method of comparing the activity of corpus luteum preparations. Such a method, used by the writer and his associates (64), yielded data in remarkable agreement with results reported by clinicians employing the same preparations.

The curious anomaly of a male genital organ exhibiting specific sensitivity for a female sex hormone, namely corpus luteum, puzzled the writer working originally on this subject. At the present time such a phenomenon is by no means an unusual one. Reference has already been made to certain "antimasculine" reactions elicited by estrogenic hormones. Again, the extensive studies on the effect of estrogenic female hormone on the estrus cycle of rats and mice, reported by numerous investigators, have eventually led to the discovery that this so called female hormone is widely distributed in nature not only among animals but also among plants and that it can be extracted in large quantities from the urine of men as well as that of pregnant women.

D. Response of fallopian tubes. The relation of the female sex hormones to the movements of the genital organs is of interest in another respect, namely, in regard to the rhythmic contractions these hormones produce in the fallopian tubes. Some of the most interesting studies reported on the subject have been those which Seckinger published from this laboratory. The effect of ovarian and corpus luteum extracts on the normal rhythmic contractions of the fallopian tubes of the pig *in vitro* was carefully observed. It was found that there was a distinct difference in the type of contractions produced by corpus luteum and whole ovary extracts, respectively. Here again, earlier experiments take on a new significance in the light of the results herein cited with regard to the relation between corpus luteum and the pharmacodynamic properties of pituitrin and epinephrin. Thus we have described at least four different smooth muscle reactions which distinguish between the follicular hormone and the hormone of corpus luteum.

7. MISCELLANEOUS EFFECTS OF CORPUS LUTEUM

A number of other physiological effects produced by female hormones in general and by

the corpus luteum in particular may be noted in this place to complete an exposition of the various reactions given by that hormone. Hisaw (34), who has done a great deal of work on female hormones, described a relaxant effect which corpus luteum extract exerted on the symphysis pubis of guinea pigs and rabbits, a relaxation similar to that occurring in all these animals during pregnancy. This reaction Hisaw found to be so characteristic that he ascribed it to the specific hormone contained in corpus luteum, which he named "relaxin."

Studies on spontaneous or voluntary activity of skeletal muscles of rats placed in rotary cages were made by Slonaker, Wang (97, 98) and associates. The latter authors first established the normal cycle of activity in rats and then studied the effects of ovariectomy and the influence of subsequent injection of various solutions of female hormones on the same animals. The results obtained were not especially significant.

A different kind of psychological study on the ovarian and corpus luteum hormones was published by Macht and Seago (61). The behavior of white rats trained in a circular maze was carefully established and their running time was measured. Ovariectomy was performed and after the rats had recovered from such an operation their muscular activity and general behavior were again observed. Small doses of ovarian and corpus luteum extracts were then injected. The results of these experiments indicated that ovarian extract in general and extract of corpus luteum definitely improved the running time and cerebral responses of both normal and ovariectomized rats.

A third reaction obtained by Macht and Matsumoto (60) with ovarian and corpus luteum extracts on the pupils of frogs' eyes may also be mentioned. These writers tested the action of 10 per cent solutions of corpus luteum and ovarian substances on frogs' eyes and noted that corpus luteum produced dilatation and the ovarian extract no effect whatever.

Finally, mention should also be made of the interesting findings reported by Kanter, Bauer, and Klawans. These writers discovered that the growth of the ovipositors of Japanese bitterlings was stimulated by feeding them with estrogenic preparations of the ovary. In this connection the present writer made some tests in which a desiccated corpus luteum preparation was fed to bitterlings by a method described elsewhere. Bitterlings placed in water containing preparations of follicular hormone showed marked elongation of the ovipositors in from 24 to 48 hours. In a series of experiments in which corpus luteum and follicular extracts, in suitable proportions, were administered simultaneously to these fish, a definite inhibition resulted; i.e., the elongation which the follicular hormone would have effected was antagonized by the corpus luteum extract and no stimulation to growth was consequently observed. Such experimentation, while not extensive, is mentioned briefly in this place (59). Kleiner and his associates have recently expressed some doubt as to the reliability of the bitterling reaction to the follicular hormone, on the one hand, and claimed, on the other, that the female bitterling is a specific physiological test animal for the *male* hormone.

EVALUATION

The abundant data, physiological and pharmacological, assembled in this paper (which, if space permitted, could be extended) afford sufficient evidence, beyond reasonable doubt, of the important endocrine function of the corpus luteum. Whether one or more hormones contained in that gland are responsible for the various physiological effects noted by different observers is not yet definitely established. Unquestionably the corpus luteum through its internal secretion plays an important rôle with regard to the course of pregnancy and in primates exerts an influence on the menstrual cycle as indicated by gross anatomical and histological changes in gonads and accessory organs. Of particular interest from the standpoint of practical therapeutics are those experiments in which corpus luteum preparations or extracts have been injected into animals, normal and castrated, for the purpose of influencing their physiological function. These indicated the close relationship and interdependence of the corpus luteum and estrogenic or follicular hormones. It

appears that these two groups of hormones in some respects exert diametrically opposite physiological effects. This antagonism is only apparent, however, and should be regarded as a synergism promoting the normal functioning of the sexual apparatus. Experimentally there is no longer any doubt as to the inhibitory effect of corpus luteum on the estrus of small animals. The most recent work on the subject corroborates this view. Thus, Dessau notes that "daily injections of estrone, estriol, or estradiol into mature guinea pigs (castrated or normal) cause proliferation and metaplastic changes of the uterine epithelium. These changes are inhibited by corpus luteum hormone." These findings are in complete agreement with the results obtained by Macht, Stickels, and Seckinger.

A discussion of the chemical nature of the various extracts or "active principles" obtained from the corpus luteum by different investigators does not come within the scope of this paper. However, although almost every investigator studying biochemical phases of the subject is inclined to regard the particular extract or preparation that he has been using as the most efficient, an impartial examination of the literature reveals that physiological effects have certainly been obtained with both the lipoid soluble and the aqueous extracts of corpus luteum.

The writer and his co-workers have experimented with all kinds of extracts prepared from corpus luteum substance. Some of these were prepared with ether, others with petroleum-ether, acetone, chloroform or ethyl acetate; and still others, with alcohol. All the extracts, prepared though they were in different ways, exhibited more or less activity when tested by various methods. The authors obtained the most satisfactory clinical results, however, with a water-soluble extract made by treating desiccated corpus luteum substance with alcohol for a prolonged period, deproteinizing it with lead acetate, filtering and removing the lead and adjusting the hydrogen-ion concentration of the resultant solution. It was found that preparations so obtained prolonged the interestrual interval in guinea pigs and rats and were also quite active in producing the peculiar and specific reactions of smooth muscle preparations from the uterus and vas deferens previously described. When the curves obtained by the writer with uterine preparations in response to posterior pituitary hormone were compared with those of other investigators, it was found that the effect produced by 1 milligram of crystalline progesterone was approximately equivalent to that resulting from repeated injections of 10 cubic centimeters of lutein solution (H.W.&D.). The author and his co-workers found furthermore that the activity of corpus luteum preparations in guinea pigs tested by the vaginal smear method ran parallel to their effects on the vas deferens of the rat, on the one hand, and on the uterus of the rabbit with respect to its response to posterior pituitary hormone, on the other. The potency of such preparations in clinical practice has been attested by reports from a host of physicians who have made carefully controlled studies on patients with all kinds of female hormone products. In the experience of the writer and his co-workers, the various physiological effects of corpus luteum were obtained not only by injection of extracts but also by prolonged feeding of desiccated corpus luteum.

Whether a single active principle or a mixture of active principles occurs in the various extracts of female gonads employed in these studies has not yet been ascertained. From the standpoint of practical therapeutics, however, the value of isolated active principles, separated from the synergistic bodies which the various glands contain in their natural state, is still debatable. Thus, for instance, the discovery and isolation of the chemically pure thyroxin, active principle of the thyroid gland, marked a great advance in biochemical science, yet in clinical practice this principle, administered alone, has proved less effective than many of the ordinary thyroid preparations on the market. The isolation and chemical identification of various vitamins marked similar progress in biological science but the value of administering minute quantities of pure vitamins, separately, in cases of defective nutrition is still disputed; in fact, such treatment has already been reported to produce dangerous pathological changes in man

and lower animals. The isolation of the various active principles of ergot scored another triumph for modern pharmacology; nevertheless, few are the skilled obstetricians who would administer small quantities of the same in preference to the well standardized galenical preparations of the drug. The chemistry of digitalis leaf, the most important heart drug at the service of the medical man, has not been entirely established. Some twenty different glucosides and other chemical bodies have been isolated from this plant and the pharmacological action of each has been carefully studied but neither digitoxin nor any other powerful pure digitaloid principle, administered separately, is as satisfactory therapeutically as the leaf itself or the official tincture and infusion of the plant.

In their search for active principles those who are interested in practical therapeutics must not lose sight of the important fact that two or more drugs may profoundly modify the action of each other in not only the pharmacological but also the physicochemical sense of the word. Thus, pharmacologically, one chemical may antagonize or potentiate the effect of another. Again, in a purely physical way, the combination or mixture of two or more bodies may serve to keep all in solution as, for instance, in case of the digitalis glucosides. The *tout ensemble* or combination of medicinal principles in the proportion in which they occur in nature is often much more effective for clinical purposes than any artificial mixture of pure principles. Such possibilities should be borne in mind when the efficiency of the female sex hormones and their preparations is considered, especially by those medical men who are interested in their practical therapeutic use. As our knowledge of the subject accumulates, we begin to doubt even such phenomena as those heretofore considered absolutely reliable criteria. Thus, for instance, in a recent paper Freed and Soskin suggest that the potency of an estrogenic substance as regards cornification bears no constant relationship to its potency as regards other important physiological properties, and therefore in their opinion an assay of estrogenic substance by the vaginal smear method alone is no absolutely reliable indicator of its potency as regards other physiological properties or as regards its possible value in therapeutics. We have not yet solved the physiological puzzle of the sexual cycle in higher animals, much less that of primates. This cycle is controlled by such an intricate and delicate system of checks and balances, depending not only on the hormones of the ovarian follicle and corpus luteum but also upon the internal secretions of the pituitary, thyroid, and suprarenal glands, that any attempt at rational substitution therapy with isolated, so called chemically pure hormones may well be considered hazardous until the whole subject of internal secretions and their physiological function is thoroughly understood. It may be much wiser for the clinical practitioner to employ carefully prepared extracts of the whole ovary or of the corpus luteum, approximating as closely as possible the normal content of the gland in its natural state unmixed with products of disintegration, rather than to experiment with combinations of allegedly "pure principles," the physiology, chemistry, and even posology of which are still unsettled.

SUMMARY

1. A résumé of all kinds of experimental data found in scientific literature regarding the physiological function of the corpus luteum is presented.

2. Three lines of investigation by the writer and his collaborators with water-soluble corpus luteum preparations are described.

3. A study of vaginal smears revealed that injections of corpus luteum extracts distinctly inhibited the estrus cycle of guinea pigs.

4. Injection of corpus luteum extracts in mice inhibited a tendency to hypertrophy of the uterus induced by injections of estrogenic follicular extracts.

5. Corpus luteum extracts elicited characteristic responses from uterine muscle of guinea pigs and cats, fallopian tubes of pigs, and vasa deferentia of white rats.

6. In the three classes of experiments the same extracts induced parallel and comparable results, thus demonstrating that the activity of corpus luteum preparations may be shown by several convenient methods.

BIBLIOGRAPHY

1. Adler, L. Arch. f. Gynaek. 1912, 95: 349.
2. Allen, E. J. Am. M. Ass., 1935, 104: 1901.
3. Allen, E., and Doisy, E. A. Physiol. Rev., 1927, 7: 600.
4. Allen, E., Pratt, J. P., Newell, Q. U., and Bland, L. J. Am. J. Physiol., 1930, 92: 127.
5. Allan, H., and Dodds, E. C. J. Obst. & Gynæc. Brit. Emp., 1930, 37: 447.
6. Antecki, S., and Zwolinski, T. Polska gaz. lek., 1928, No. 46: 345.
7. Aschheim, S. Med. Klin, 1926, 22: 2033.
8. Bouin, P., Ancel, P., and Villemin, F. Compt. rend. Soc. de biol., 1906, 61: 417.
9. Bracht, R. Therap. d. Gegenw., 1933, 74: 551.
10. Brouha, L., and Simonnet, H. Compt. rend. Soc. de biol., 1929, 101: 366.
11. Bucura, C. J. Ztschr. f. Heilk, 1907, 28: 147.
12. Corner, G. W. J. Am. M. Ass., 1935, 104: 1899.
13. Corner, G. W., and Allen, W. M. Am. J. Physiol., 1929, 88: 326.
14. Corner, G. W., and Hurni, F. H. Am. J. Physiol., 1918, 46: 483.
15. Courrier, R. Compt. rend. Soc. de biol., 1924, 90: 453.
16. Idem. Arch. de biol., 1924, 34: 369.
17. De Fremery, P., Luchs, A., and Tausk, M. Arch. f. d. ges. Physiol., 1932, 231: 341.
18. Dessau, F. Arch. internat. de pharmacod., 1934, 55: 402.
19. Falls, F. H., Lackner, J. E., and Krohn, L. J. Am. M. Ass., 1936, 106: 271.
20. Fellner, O. O. Arch. f. d. ges. Physiol., 1921, 189: 199.
21. Idem. Arch. f. Gynaek., 1923, 120: 231.
22. Ibid. 1913, 100: 641.
23. Foster, M. A. Anat. Record, 1933, 55: 56.
24. Frank, R. T., and Rosenbloom, J. Surg., Gynec. & Obst., 1915, 21: 646.
25. Fraenkel, L. Arch. f. Gynaek., 1903, 68: 438.
26. Freed, S. C., and Soskin, S. Endocrinology, 1936, 20: 863.
27. Glismann, M. B. J. Oklahoma M. Ass., 1928, 21: 212.
28. Haberlandt, L. Klin. Wchnschr., 1923, 2: 1938.
29. Idem. Arch. f. d. ges. Physiol., 1927, 216: 525.
30. Halban, J. Muenchen. med. Wchnschr., 1921, 68: 1314.
31. Herrmann, E. Monatschr. f. Geburtsh. u. Gynaek., 1915, 41: 1.
32. Herrmann, E., and Stein, M. Zentralbl. f. Gynaek., 1920, 44: 1449.
33. Hirst, J. C. A Manual of Gynecology. Philadelphia: W. B. Saunders Co., 1925.
34. Hisaw, F. L. Physiol. Zool., 1929, 2: 59.
35. Hisaw, F. L., Meyer, R. K., and Fevold, H. L. Proc. Soc. Exper. Biol. & Med., 1930, 27: 400.
36. Hofbauer, J. Zentralbl. f. Gynaek., 1920, 44: 777.
37. Holtz, P. Verhandl. d. deutsch. pharmakol. Gesellsch., 1936, 13: 74.
38. Iscovesco, H. Compt. rend. Soc. de biol., 1912, 73: 16, 104.
39. Jentzner, A., and Buettner, O. Ztschr. f. Geburtsh. u. Gynaek., 1900, 42: 66.
40. Kanter, A. E., Bauer, C. P., and Klawans, A. H. J. Am. M. Ass., 1934, 103: 2016.
41. Kaufmann, C. Zentralbl. f. Gynaek., 1933, 57: 42.
42. Kelly, G. L. Surg., Gynec. & Obst., 1931, 52: 713.
43. Kennard, J. H. Am. J. Physiol., 1937, 118: 190.
44. Kennedy, W. P. Quart. J. Exper. Physiol., 1925, 15: 103.
45. Kleiner, I. S., Weisman, A. I., and Mishkind, D. I. Zoologica, 1936, 21: 241.
46. Knab, F. Zentralbl. f. Gynaek., 1933, 57: 987.
47. Knaus, H. Arch. f. d. ges. Physiol., 1924, 203: 394.
48. Idem. Arch. f. Gynaek., 1929, 138: 201.
49. Ibid., 1930, 140: 181; 141: 374, 395.
50. Idem. Arch. f. exper. Path. u. Pharmakol., 1930, 151: 371.
51. Idem. Muenchen. med. Wchnschr., 1928, 75: 553.
52. Kochmann, M. Arch. f. exper. Path. u. Pharmakol., 1928, 137: 187.
53. Ibid., 1929, 143: 57.
54. Krohn, L., Falls, F. H., and Lackner, J. E. Am. J. Obst. & Gynec., 1935, 29: 198.
55. Lane-Claypon, J. E., and Starling, E. H. Proc. Roy. Soc., 1906, B. 77: 505.
56. Loeb, L. Surg., Gynec. & Obst., 1917, 25: 300.
57. Loewe, S. Handb. d. norm. u. path. Physiol., 1926, 14: 501.
58. Long, J. A., and Evans, H. M. Mem. Univ. Calif., 1922, 6: 1.
59. Macht, D. I., and Bryan, H. F. Am. J. Physiol., 1936, 116: 103.
60. Macht, D. I., and Matsumoto, S. Endocrinology, 1919, 3: 154.
61. Macht, D. I., and Seago, D. W. J. Comp. Psychol., 1924, 4: 151.
62. Macht, D. I., and Stickels, A. E. Proc. Soc. Exper. Biol. & Med., 1930, 27: 427.
63. Ibid., 1931, 28: 801.
64. Macht, D. I., Stickels, A. E., and Leach, H. P. Proc. Soc. Exper. Biol .& Med., 1929, 27: 152.
65. Macht, D. I., Stickels, A. E., and Seckinger, D. L. Am. J. Physiol., 1929, 88: 65.
66. Makepeace, W., Corner, G. W., and Allen, W. M. Am. J. Physiol., 1936, 115: 376.
67. Manzi, L. Arch. di ostet. e. ginec., 1932, 19: 220.
68. Marshall, F. H. A. Physiology of Reproduction. New York and London: Longmans, Green & Co., 1922.
69. Matsumoto, S., and Macht, D. I. J. Urol., 1919, 3: 63.
70. Miklos, L. Zentralbl. f. Gynaek., 1930, 54, 1755.
71. Okintschitz, L. Arch. f. Gynaek., 1914, 102: 333.
72. Papanicolaou, G. N. Proc. Soc. Exper. Biol. & Med., 1924, 22: 106.
73. Idem. J. Am. M. Ass., 1926, 86: 1422.
74. Parkes, A. S., and Bellerby, C. W. J. Physiol., 1926, 62: 145.
75. Pearl, R., and Surface, F. M. J. Biol. Chem., 1914, 19: 263.
76. Pincus, G., and Werthessen, C. B. Am. J. Physiol., 1937, 120: 100.
77. Pratt, J. P. Endocrinology, 1927, 11: 195.
78. Reynolds, S. R. M. Am. J. Physiol., 1930, 92: 420; 1931, 97: 706.
79. Robson, J. M., and Illingworth, R. E. J. Exper. Physiol., 1931, 21: 93.
80. Saiki, Seiichi. Am. J. Physiol., 1932, 100: 8.
81. Seckinger, D. L. Bull. Johns Hopkins Hosp., 1923, 34: 236.
82. Idem. Am. J. Physiol., 1924, 70: 538.
83. Seitz, L., Wintz, H., and Fingerhut, L. Muenchen. med. Wchnschr., 1914, 61: 1657, 1734.
84. Shickele, G. Biochem. Ztschr., 1912, 38: 169, 191, 214.
85. Idem. Ztschr. f. d. ges. exper. Med., 1913, 1: 539.
86. Siddall, A. C. J. Am. M. Ass., 1928, 90: 380.

87. SIDDALL, A. C. J. Am. M. Ass., 1928, 91: 779.
88. SLONAKER, J. R. Am. J. Physiol., 1924, 68: 294.
89. SMITH, P. E., and ENGLE, E. T. Proc. Soc. Exper. Biol. & Med., 1932, 29: 1025.
90. SMITH, G. V. S., and SMITH, O. W. J. Am. M. Ass., 1931, 97: 1857.
91. SONNENBERG, N. Berl. tieraerztl. Wchnschr., 1907, No. 39: 700.
92. STEINACH, E., and HOLZKNECHT, G. Arch. f. Entwcklngsmechn. d. Organ., 1916, 42: 490.
93. STOCKARD, C. R., and PAPANICOLAOU, G. N. Am. J. Anat., 1917, 22: 225.
94. VAN DYKE, H. B., and GUSTAFSON, R. G. J. Pharmacol. & Exper. Therap., 1929, 37: 379.
95. VOSS, H. E. Arch. f. d. ges. Physiol., 1927, 216: 156.
96. WAGNER, G. A. Deutsche med. Wchnschr., 1932, 58: 964.
97. WANG, G. H. Comp. Psychol. Mon., 1923, 2: 1.
98. WANG, G. H., RICHTER, C. P., and GUTTMACHER, A. F. Am. J. Physiol., 1925, 73: 581.
99. WEINZIERL, E. Med. Klin., 1933, 29: 563.
100. WERNER, A. A., and COLLIER, W. D. J. Am. M. Ass., 1933, 100: 633.
101. WOLFSON, H. Med. Welt., 1932, 6: 1616.
102. ZONDEK, B., and ASCHHEIM, S. Klin. Wchnschr., 1926, 5: 2199.
103. ZONDEK, B., and ASCHHEIM, S. Endokrinologie, 1928, 1: 10.

EXPERIMENTAL CHOLECYSTITIS

HANS G. ARONSOHN, M.D., and EDMUND ANDREWS, M.D., F.A.C.S., Chicago, Illinois

A REVIEW of the literature on the etiology of gall-bladder diseases reveals that 9 of 10 publications consider bacterial infection to be the most likely agent. Some uncertainty as to the accuracy of this view is evident, however.

The first to associate gall-bladder inflammation with infection was John Hunter, who first observed cholecystitis in typhoid fever patients. Gilbert and Girode proved this relationship bacteriologically, while Chiary added clinical evidence in support of this view. The idea was quick to take and was soon confirmed by many authors. Doubt, however, was early expressed, Rolleston emphasizing the need for an additional factor than infection, basing his idea on the clinical fact that cases of cholecystitis were increasing coincident with a marked decrease in the occurrence of typhoid fever. This is confirmed by Osler's report of 19 cases of cholecystitis in a series of 1,500 cases of typhoid fever, while it is well known that most cases of typhoid fever have a large number of organisms in the bile. Furthermore, the theory of the relationship between typhoid fever and gall-bladder disease was an intimate one, and received its death blow in the fact that the former has practically disappeared from all civilized communities without any appreciable lessening in the evidence of gall-bladder disease.

Organisms other than typhoid bacilli have also been incriminated. Much valuable information was obtained by culturing the bile and the walls of gall bladders obtained at post mortem examinations and at operation. Table I is taken from the article by Rehfuss and Nelson (45), and needs little comment. Both Andrews (3) and Magner, studying the content of human gall bladders removed at operation, have found 65 per cent of cases to contain sterile bile. Osler places this figure at 52 per cent. According to the study of Magner and Hutcheson, Bacillus coli is the most common organism in the cavity of the gall bladder, while streptococci are found more often in the gall-bladder wall. Drennan emphasizes the anti-bacterial activity of bile on account of his small percentage of positive cultures. Scarcity of clinical signs of infection, the low fever, the mild leucocytosis, and the rareness of leucocytes in the bile convinced Denton that infection does not play a primary rôle in the production of cholecystitis. Feinblatt concurs in this opinion on the basis of the slight inflammatory changes he observed in the gall-bladder wall and the small amount of leucocytes in the bile. In contrast to this idea, Hunlemueller found positive bacterial cultures in 100 per cent of cases when he included both the gall-bladder wall and the liver. The finding by Koch and Chiarolanza of emboli in the folds of the mucous membrane led to the conclusion that a transverse infection of the wall is the usual route.

From the Department of Surgery, University of Chicago. This work has been aided by a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

EXPERIMENTAL LITERATURE

The amount of experimental work done to prove the theory of infection as playing the leading part in the etiology of cholecystitis is enormous. Most authors have tried to confirm their clinical observations by animal experimentation. The various techniques employed are emphasized in the following discussion, as differences in results might be due in some cases to variations in the methods employed.

Intravenous injection of bacteria has been a popular method. Bacillus typhosus was found in the bile fairly regularly by Blackstein several days or weeks following intravenous injection of this organism. Sherrington, using Bacillus anthracis, Bacillus pyocaneus, and staphylococci, recovered the organisms in the bile in only 18 out of 49 cases. The condition of the walls of the gall bladders was not mentioned in these experiments. Gilbert (23) considered Bacillus coli the most important

factor in producing cholecystitis. Many authors have inoculated the bacteria directly into the wall and cavity of the gall bladder. The results obtained in these cases are even more contradictory. Cushing, using typhoid bacilli injected into the rabbit's gall bladder, and Italia, using Bacillus coli and Bacillus typhosus in both rabbits and dogs, obtained inflamed gall bladders with stone formation. Rosenow, working on his idea of the "selective affinity" of bacteria (especially streptococcus and Bacillus coli) to certain organs and tissues, tried to establish a connection between "foci of infection" and gall-bladder disease. He used both the intravenous and the direct inoculation methods, and obtained contradictory results, as in certain cases in which the intravenous route produced marked cholecystitis, direct inoculation into the gall bladder was ineffective. Schoebl was more successful in producing cholera carriers by direct inoculation than by intravenous injection. Meyer and coworkers, using typhoid bacilli, obtained positive results with both methods.

Doerr observed that excretion of typhoid bacilli into the bile, which occurred regularly after the injection of the former into the systemic veins, could be prevented by ligation of the cystic duct. Koch and Chiarolanza, however, arrived at opposite conclusions. They found typhoid bacilli in the gall bladder after intravenous injection even after a preceding cystic duct ligation.

Nichols produced "lesions of the gall bladder" in a high percentage of cases by injecting typhoid bacilli into the mesenteric or ear veins. Emmerich and Wagner obtained similar lesions by direct inoculation of typhoid bacilli into the rabbit's gall bladder. Venema's experiments, however, performed under similar conditions, revealed no changes in the gall bladder.

In connection with the "specific affinity" idea of Rosenow we ought to mention the work of Brown, who found mainly streptococci in the emulsified gall-bladder tissue from cases of human cholecystitis. He demonstrated serologically the direct etiological importance of these streptococci and proved their specific affinity for the gall bladder by intravenous injection in rabbits.

Staphylococci are used in the experimental work of Magner and Hutcheson. These authors produced a change in the gall bladder wall by injecting these organisms under the serous layer, while this change occurred in only a limited number of cases following injection into the lumen.

More recently Rehfuss and Nelson studied the problem of gall-bladder infection in the experimental animal and concluded that a variety of organisms when injected intravenously in the rabbit, can produce lesions of the gall bladder.

Evidence other than infection in the literature. Much doubt has been expressed on different occasions on the accuracy of the theory that infection plays the primary rôle in the etiology of gall-bladder lesions. Clinical observations caused various authors to search for some other cause.

On the basis of his clinical observations, Denton was not able to accept the theory of infection and suggested mechanical and circulatory disturbances as the causes of the gall-bladder pathology. Similarly Feinblatt concludes from his pathological studies that mechanical and metabolic factors are important parts in the production of cholecystitis.

One metabolic disturbance in particular has found a prominent place in the literature in this connection, i.e., the cholesterol metabolism. The "strawberry gall bladder," first described by Moynihan occurs under certain pathological conditions of cholesterol metabolism. Boyd considers infection to be the cause of this metabolic disturbance. Wilkie and Rosenow obtained positive cultures from the wall, the gall-bladder contents and stones of such cases. The importance of cholesterol in stone formation is well known and need not be taken up here. There is no evidence, however, in the literature, of acute inflammatory changes in the gall-bladder wall in connection with a disturbance in cholesterol metabolism.

As compared to the enormous amount of literature on cholecystitis brought about experimentally by bacterial infection, relatively little is known about chemical cholecystitis.

Well known is the work of Mann, who produced acute changes in the gall-bladder

wall by the intravenous injection of Dakin's solution. Dilatation of the lymphatics, breaking-down by blood, are the typical microscopic changes. In another series of experiments, changes of the gall-bladder wall were brought about by the direct introduction of chemically or mechanically irritating substances, as for instance mustard oil, used by Darnbacher and Sacks.

The effect of x-ray radiation was shown by Brams and Darnbacher to consist of an acute inflammatory change in the gall-bladder wall.

PHYSIOLOGY OF THE GALL BLADDER

Any discussion of the problem of gall-bladder diseases requires first a precise knowledge of the function of liver cells as well as the chemical and biological characteristics of bile. The gall bladder is more than a container to store bile. We know from the extensive investigations of Peyton, Rous, and McMaster that the gall bladder concentrates liver bile to a great extent. Andrews (2) has shown that the function which the human gall bladder performs has been greatly underestimated. This fact is of importance for the proper understanding of the disorders of function which are often found after cholecystectomy. The gall bladder ought not to be considered as just a useless appendix to the liver which can be removed without any risk. Bile itself offers many biochemical problems. The extensive use of bile as a medium for culturing bacteria is well known. However, there is no uniform behavior, for while bile favors the growth of certain organisms, it has an inhibitory effect on others.

The greatest difficulty arises in studying the chemical composition of bile. Cholesterol, bilirubin, and calcium have been studied by many authors in connection with stone formation and pregnancy.

Modern investigation has shown that cholesterol is kept in solution by bile acids and that precipitation of cholesterol occurs when the bile acids are diminished.

While biochemists are studying the various fractions and chemical formulas of bile salts, very little is known about their biological importance. The modern conception is that the bile salts are produced in the reticulo-endothelial system, excreted by the liver, concentrated in the gall bladder, excreted into the intestines, and reabsorbed by way of the portal system. Their function in emulsifying fats is well known but very little else about their normal functions is known. It is, therefore, not surprising that still less is known about the rôle they play under pathological conditions.

PATHOLOGICAL ANATOMY

Little information is added from anatomical studies as to the etiology of cholecystitis.

Gall bladders, removed at operation for acute gall-bladder disease, often prove to be either perfectly normal at microscopic examination or show changes which are in no way sufficiently characteristic to classify them into one pathological group.

However, in a great number of cases a definite anatomical picture is found. We will give a short description of these lesions to serve as a comparison with the results obtained in experimental work.

Henke and Lubarsch compare the findings in acute cholecystitis with those found in acute appendicitis, the purulent infiltration of the wall, however, being less pronounced in the former case. The character of the exudate is seropurulent. The process begins in the intramuscular pits of the mucous membrane, the so called *Luschkaschen Gaenge*. Later, the entire wall, especially the serosa, becomes involved. Thickening of the gall bladder is due mainly to edema in the outer layers.

The description given by modern American authors, such as Graham, Boyd, Andrews, Feinblatt, and others, differs in that the presence of pus cells in acute cholecystitis is practically denied. Edematous thickening of the serosa with round cell infiltration, dilatation of the lymphatics and deposition of a fibrinous exudate on the serosa are the common findings. The mucosa is very often normal, while some round cell infiltration is often found in the muscularis.

REASONS FOR A NEW APPROACH TO THE PROBLEM

From this review of the literature on cholecystitis one can see the confused status of

present opinion on the subject. The theory of infection is questioned, but while other theories are suggested, none is actually proved.

Experimental results vary considerably, and often are even contradictory. This may be due to differences in the technique employed by various investigators.

The disadvantage of the most commonly used method, i.e., introduction of bacteria by means of a needle puncture through the gall-bladder wall, was recognized by many early workers. Rosenow found damage to the gall-bladder wall, in many instances, at the point of injection. Venema found this damage to be severe in extent, an observation which is confirmed by Wilkie.

Venema then tried to improve the needle puncture technique by cauterizing the wall at the point of injection. He obtained normal gall bladders in this way, while Emmerich and Wagner had produced changes of the wall. Hospers performed the injection through the liver surface of the gall bladder, a method which leaves the free surface unharmed but may cause occasional bleeding in the liver tissue.

Intravenous injection of bacteria as practiced by Rosenow and others is a much more satisfactory method. Positive reactions in the gall bladder after such injection seem to indicate a specific affinity of these bacteria for the biliary system. Negative results, however, are of lesser value, since we have no way of proving that the organisms actually reached the gall bladder. They might still possess some definite affinity for the gall bladder if brought there in some other way. Another disadvantage of the intravenous method is the bacteriemia which is produced, and which is usually not present in human cholecystitis.

In the production of experimental cholecystitis the dosage used in most cases has been so extreme that it can hardly be compared to any possibility offered by focal infection in man. Several observers have stated that the liver was a rather efficient filter for bacteria in the blood and that only when overwhelming doses were given did any appear in the bile. Furthermore some state that trauma must be added to cause infection to spread from bile to gall bladder if injection be made locally.

We have often made the observation in sampling the gall bladders of dogs that the needle punctures were seen to react sharply. The next day there is usually an area about a centimeter in diameter which histologically closely resembles acute cholecystitis. For these reasons the development of a special technique was important. Needle puncture is, of course, ruled out. Closure of the ducts alone has previously been shown to cause severe damage to the gall-bladder wall. Therefore the following technique was adopted.

A NON-TRAUMATIZING TECHNIQUE

Experimental cholecystitis from which conclusions can be drawn concerning human cholecystitis, requires 3 basic postulates: (1) the cholecystitis must be a direct result of the material used; (2) the material introduced must be such as is normally found either in the body fluid or in the ingested food and should not be artificial and foreign to the body; (3) the reaction produced in the experimental animal must be similar in appearance to human cholecystitis.

We have found a technique which fulfills the third requirement in a satisfactory manner. The principle of our technique is the retrograde introduction of a fine ureter catheter into the gall bladder through an opening in the common duct and the subsequent plastic repair of the duct by insertion of a glass cannula.

A detailed description of this technique, which was applied in dogs only, follows.

The dog's abdomen is opened under ether anesthesia by an incision in the upper midline, the duodenum is lifted aside, and the common duct is freed by blunt dissection from the surrounding tissue. A longitudinal incision, about 1 centimeter long is made in the duct about 1.5 centimeters distant from its entrance into the duodenum, and the margins of this opening are clamped by a mosquito forceps. A soft French rubber catheter, 2.5 to 3.5 millimeters in diameter is then introduced through this opening into the gall bladder. Bile is aspirated and the particular material we are testing is injected into the gall bladder through this catheter. Before the catheter is withdrawn and the glass cannula is inserted,

Fig. 1a. Microscopic appearance 48 hours following the introduction into the gall bladder of commercial bile salts 15 per cent. Note edematous thickening of the serosa five times normal with fibropurulent exudate on serosal surface.

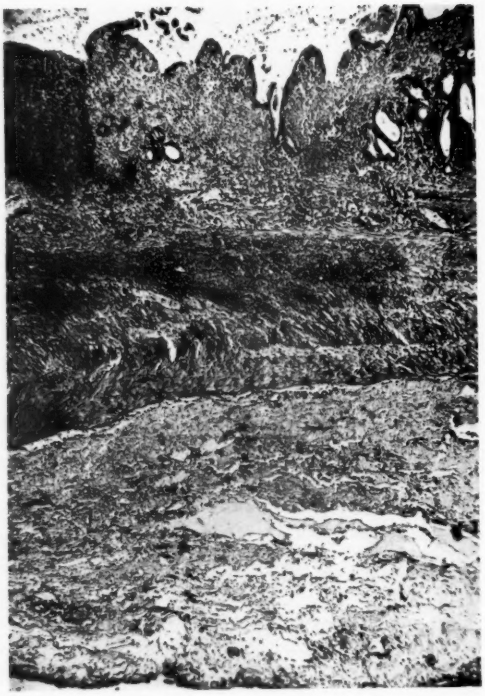


Fig. 1b. Microscopic appearance 48 hours following the introduction into the gall bladder of sodium desoxycholate 8 per cent. Diffuse leucocytic infiltration of all three layers.

a rubber protected clamp is placed around the common duct as close to the gall bladder as possible. This is necessary to prevent a back flow of bile.

The cannula, which is 3 centimeters in length and 4 millimeters in diameter, tapering at the ends and grooved transversely a short distance from the tips on each side, is inserted into the common duct and kept in place tightly by 2 ligatures around the grooved surfaces. After the duct is unclamped and a rather normal bile flow is observed, the edges of the opening are sutured together above the cannula.

Since, during the whole procedure, which takes about 20 minutes, the gall bladder is not even brought into view, we feel sure that the factor of traumatization is practically negligible.

That this is actually the case has been proved by a great number of control experiments. In some cases bile was aspirated and nothing injected, while in others the gall bladder was thoroughly washed with normal saline solution. The animals were electrocuted 24 or 48 hours after operation and the gall bladders were found to be perfectly normal on gross and microscopic examination.

Absence of reaction in the gall bladder shows that, by use of the technique described, experimental manipulation of the gall bladder is possible without any traumatization.

THE THEORY OF INFECTION AND THE OBJECTIONS TO IT

The main arguments against the infectious theory of cholecystitis, based on anatomical and clinical observations are summarized as follows:

1. Pathological studies of diseased gall bladders reveal few signs of bacterial infec-

tion. Mononuclear cells are prevalent, while pus cells are rarely found, not even in cases of so called "empyema," in which the gall bladder content usually consists of amorphous débris or cholesterol crystals rather than of true pus.

2. Bacteria are seldom found in stained sections of the gall-bladder wall and the bile is found to be sterile in a high percentage of diseased gall bladders.

3. Finally there is the clinical observation that sepsis is a rare complication of cholecystitis and that the gall bladder is rarely involved in cases of pyemia.

To prove or disprove the infectious theory, the following series of experiments were carried out:

Bacteria obtained from human sources, such as acute and chronic mastoiditis, sinusitis, adenitis, etc., were introduced into the gall bladders of dogs by means of the catheter-cannula technique. The cultures were of recent isolation. The bacteria used for the injection were suspended in saline solution in a concentration of approximately 500 million bacteria per cubic centimeter, the criterion used being the cloudiness of the suspension as compared with one of known bacterial content. One cubic centimeter of this suspension was the amount generally injected. Wherever the reaction obtained was especially severe, the experiments were repeated with smaller amounts, while 2 or 3 cubic centimeters were injected in cases in which no reaction occurred.

Tables I, II, and III give detailed description of the 26 experiments.

Cholecystitis 1 indicates a gall bladder with only few changes, slight edema, and congestion in the serosa being the only pathological findings.

In cholecystitis 2, the gall-bladder wall was thickened up to 4 millimeters, the acute inflammatory signs were more definite, and a thin fibrinous membrane covered the serosa.

Cholecystitis 3 includes all those cases in which the changes exceed those in group 2 as to thickness of the wall and the extent of inflammatory signs. Whenever the introduction of the catheter or the insertion of the cannula was attended with difficulty, the term "traumatization" was included in the column labeled "complications." Wherever this happened, or in those experiments in which the common or cystic duct was tied, results are of value only when the gall bladder remained normal in spite of the bacterial injection or duct ligation or traumatization.

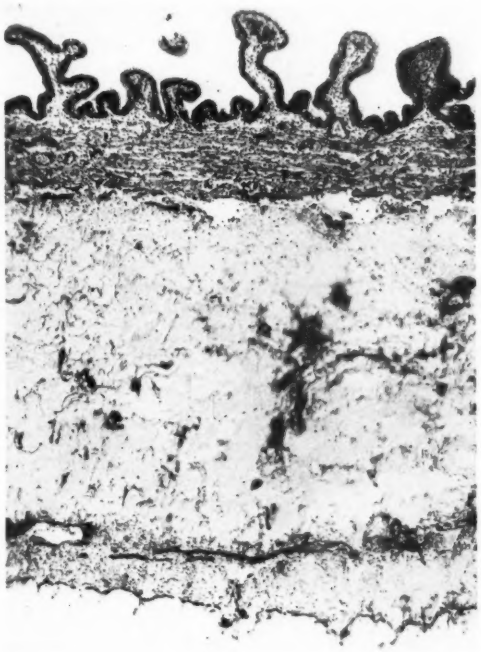


Fig. 2. Microscopic appearance 20 minutes following the intravenous injection of commercial bile salts. Marked edema of serosa about four times normal thickness.

RESULTS

Special emphasis is laid in our experiments upon the studying of Streptococcus hemolyticus, which has been accused of being the main causative agent in the production of cholecystitis in both animal experimentation and in man. Four different strains of Streptococcus hemolyticus were used in 12 injection experiments. Although three of the four strains were taken from acute human infectious processes, changes of the gall-bladder wall occurred in only one of these.

These changes, however, occurred in all 3 of the cases, in which this particular strain

TABLE I. REVIEW OF 4,395 CASES OF CHOLECYSTITIS*

Bacterial Study in 2,162 Cases, Exclusive of Rovsing's 530 Cases

Author	No. Cases	Wall culture	Contents cultures	Stones present	Stones cultures	Acute cases	Acute cultures	Chronic cases	Chronic cultures	Predominating organism in order of frequency
Blalock	270		58							B. coli, 49%; B. typhosus, 19%; Staphylococci, 12%; Streptococcus non-hem. 3%; B. coli and Streptococcus non-hem., 4%. Other cases collected from 1889 to 1925 at Johns Hopkins
Branch	210	53		94	27	57	42	153	11	B. coli, Staphylococcus, Streptococcus
Brown	70	36				20	15	50	21	Streptococcus, B. coli
Burden	17		Cholecystitis is not usually the result of an acute process but rather a result of mild infection—slowly affecting different layers of the gall bladder. Chronicity is favored by the anatomy and histology of the organ, which predisposes to stasis and obstruction							
Deaver (1)	57	30 (24 positive cystic nodes, 6 negative cystic nodes)	7							
Deaver (2)	903	No bacteriological study made		451	Conception—modern opinion—primary hepatitis often preceded by appendicitis					
Denton	403			188	Failure to demonstrate lesions primarily bacterial in origin leads author to conclude that factors other than infection (mechanical and circulatory) are necessary for explanation of the majority of lesions commonly observed in the gall bladder					B. coli or Gram positive bacillus in 4 of 94 paraffin sections
Drennan	100	84								B. coli, Staphylococcus, Streptococcus
Feinblatt	400			240	A pathological study leads one to believe that the rôle of infection in the causation of cholecystitis has been greatly overestimated—while the importance of the metabolic and mechanical factors has not received due consideration.					B. coli predominating in pus of 20 (empyema) cases
Friesleben	132	73 of 96 exam.	62 of 132 exam.							B. coli
Gordon-Taylor and Whitby	50	41	16	50	14					B. coli, 30%; Streptococcus fæcalis, 28%; B. welchii, 18%; Staphylococcus, 13%; others, 4%
Illingworth	100	62	40	62	7	12	10	88	52	Streptococcus, B. coli, Staphylococcus
Johnson	100	31	32	66	16	20	13	78	18	B. coli, Staphylococcus, Streptococcus
Judd	200	98	28 of 197 exam.	107	24 of 64 exam.					Streptococcus, B. coli, Staphylococcus
Kelly	240	113								B. coli, B. typhosus, Staphylococcus aureus
Magner and Hutcheson	200	178		119						Streptococci (typical 12-5%); B. coli, 26% (atypical Staphylococcus, 17%); others, 19%
Magner and Hutcheson			34 of 105 exam.							B. coli, 17-9%; Streptococci (typical, 2-8%); Staphylococci (atypical, 3-7%); others, (5-6%)
Moynihan	81	30	25							
Rosenow	76	51 of 64 exam.	30 of 64 exam.		57 of 92 exam.					Streptococcus, B. coli
Rovsing	530			530	216					
Williams and McLachlan	106	50 of 96 exam.	43 of 93 exam.	47	14	4	3	93	43 of 84 exam.	B. coli, Enterococcus, Staphylococcus, B. welchii, and others
Wilkie (1)	50	6	6							Streptococcus, B. coli from 4 to 5 cystic glands—43 streptococci
Wilkie (2)	100	84								Streptococcus viridans

*Rehfuss and Nelson. Am. J. Digest. Dis., 1935, 1: 764.

TABLE IA.—STREPTOCOCCUS HÆMOLYTICUS*

Experiment No.	Strain injected	Amount	Method of introduction	Duct open except where ligation stated	Complications and results
1	Acute mastoiditis, 1	0.5 c.cm.	Catheter	Cannula	Dying when electrocuted. Cholecystitis 3, bile peritonitis
2	Acute mastoiditis, 1	3 drops	Catheter	Cannula	Died. Cholecystitis 3, postmortem changes
3	Acute mastoiditis, 1	3 drops	Catheter	Cannula	Very sick. Cholecystitis 2–3
4	Acute sinusitis	2 c.cm.	Catheter	Cannula	Gall bladder normal
5	Acute sinusitis	1 c.cm.	Catheter	Cannula	Gall bladder about normal
6	Acute sinusitis	2 c.cm.	Catheter	Cannula	Gall bladder normal
7	Acute sinusitis	1 c.cm.	Catheter	Cannula	Cholecystitis 1
8	Acute sinusitis	1 c.cm.	Needle puncture	Common duct ligation	Thickening of gall-bladder wall
9	Acute sinusitis	1 c.cm.	Catheter	Cannula	Gall bladder about normal
10	Acute mastoiditis, 11	1 c.cm.	Catheter	Cannula	Gall bladder normal
11	Acute mastoiditis, 11	1 c.cm.	Catheter	Cannula	Gall bladder normal
12	Chronic mastoiditis	1 c.cm.	Catheter	Cannula	Gall bladder normal

*Streptococcus hæmolyticus in strain from: (1) acute mastoiditis, 3 dogs; (2) acute sinusitis, 6 dogs; (3) acute mastoiditis 11, 2 dogs; (4) chronic mastoiditis, 1 dog.

had been injected. Death of the animal within 15 hours after injection resulted in one instance, while another animal was moribund in 24 hours, and the third one in very poor condition when killed.

In contrast to these experiments the dogs into which the other three strains of Streptococcus hemolyticus were injected, showed no signs of illness. Postmortem examination after electrocution revealed either normal gall bladders or changes which were very slight and not of an inflammatory character.

Table II shows that Bacillus coli has no effect on the gall-bladder wall. This chart demonstrates clearly the value of a proper technique. In two animals where traumatization occurred or duct ligation had been performed, severe reactions were produced, which cannot be attributed to the action of the bacteria, since bacterial injection by means of the catheter-cannula technique revealed definitely negative results.

Similarly we conclude from Table III that none of the organisms used in this series can produce cholecystitis.

On microscopic examination, we find in the gall bladders, where the strain of Streptococcus hemolyticus from acute mastoiditis had been injected, an enormous thickening of the serous layer, which is mainly due to edema and hyperemia. The serosa is infiltrated with leucocytes and covered with a fibrinous exudate. Those gall bladders, however, into which had been injected another strain of Streptococcus hemolyticus or any of the other bacteria named in the charts either proved to be normal or revealed only very slight changes.

In summarizing these experimental results we may conclude that there is little tendency for acute bacterial infection of the gall-bladder wall to result from any of the contents of the organ. Bacteria, although present in bile in

TABLE II.—BACILLUS COLI

Experiment No.	Bacillus Coli c.cm.	Method of introduction	Duct open except where ligation stated	Complications and results
1	1	Catheter	Cannula	Gall bladder normal
2	1	Catheter	Cannula	Gall bladder normal
3	2	Catheter	Cannula	Gall bladder normal
4	1	Catheter	Cannula	Some traumatization. Cholecystitis 1
5	1	Needle puncture	Common duct ligation	Some traumatization, died. Cholecystitis 3, postmortem change, bile peritonitis
6	1	Needle puncture	Common duct ligation	Very sick. Dilated gall bladder with fibrinous exudate
7	1	Needle puncture	Common duct ligation	Gall bladder about normal
8	1.5	Needle puncture	Cystic duct ligation	Slight reaction on gall bladder

TABLE III.—MISCELLANEOUS BACTERIA*

Experiment No.	Bacteria injected	Amount in c. cm.	Method of introduction	Duct open except where ligation stated	Complications and results
1	Staphylococcus albus	1	Catheter	Cannula	Gall bladder normal
2	Staphylococcus albus	1	Needle puncture		Gall bladder normal
3	Staphylococcus albus	1	Needle puncture	Cystic duct ligation	Traumatization. Slight reaction on gall bladder
4	Staphylococcus aureus	1	Catheter	Cannula	Gall bladder normal
5	Staphylococcus aureus	1	Catheter	Cannula	Gall bladder about normal
6	Staphylococcus aureus	2	Catheter	Cannula	Gall bladder normal
7	Staphylococcus aureus	2	Catheter	Cannula	Bile peritonitis, some reaction on gall bladder
8	Staphylococcus aureus	2	Needle puncture		Slight reaction on gall bladder
9	Staphylococcus aureus	1	Catheter	Common duct ligation	Died. Cholecystitis 3, postmortem changes
10	Streptococcus viridans	1	Catheter	Cannula	Gall bladder about normal
11	Streptococcus viridans	1	Catheter	Cannula	Gall bladder normal, some bile peritonitis
12	Streptococcus viridans	2	Catheter	Cannula	Gall bladder normal
13	Bacillus welchii	1	Catheter	Cannula	Gall bladder normal
14	Bacillus welchii	0.5	Catheter	Cannula	Gall bladder normal
15	Bacillus welchii	1	Catheter	Common duct ligation	Traumatization died. Postmortem change on gall bladder
16	Bacillus welchii	0.5	Needle puncture	Common duct ligation	Gall bladder about normal

*(1) Staphylococcus albus, 3 dogs; (2) Staphylococcus aureus, 6 dogs; (3) Streptococcus viridans, 3 dogs; (4) Bacillus welchii, 4 dogs.

overwhelming numbers, do not cause any change in the gall-bladder wall, unless they are of unusually great virulence.

These results concur with the observations of Rosenow and of Magner and Hutcheson, who stressed the varying activity within the Streptococcus hemolyticus group on the basis of differences in virulence. The negative results, however, which we obtained in using Bacillus coli, stand in direct disagreement both with the clinical data reported by Gilbert and the experimental work done with this organism by Italia. The negative results after the injection of Staphylococcus albus and aureus, Streptococcus viridans and Bacillus welchii agree with results reported in the literature.

CHEMICAL CHOLECYSTITIS

Mechanical factors can produce lesions in a gall bladder containing stones. There is little doubt that the presence of one or more stones in the gall bladder or the impaction of a stone in the cystic or common duct can lead to marked changes in the gall-bladder wall. However, at postmortem examination, stones are often found in patients who, during life, never had any gall-bladder symptoms, and many stone-containing gall bladders reveal no anatomical changes in their walls. This would suggest that mechanical interference as represented by the presence of stones can be considered an aggravating, but not a primary, factor in the production of gall-bladder lesions.

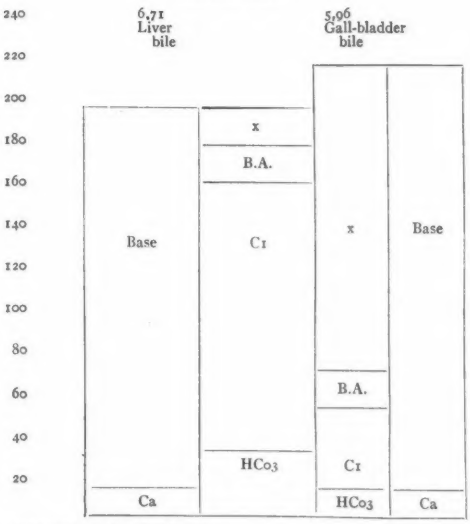
There is even less support for the theory of mechanical cholecystitis in a gall bladder without stones. Cases of gall-bladder disease after external injury are as rare as traumatic appendicitis. The gall bladder is deeply imbedded in the liver and well protected against injuries from the outside; hence cholecystitis on a purely mechanical basis in the stoneless gall bladder cannot be accepted.

In considering the possible chemical agents as etiological factors, there are as many possibilities as there are constituents in bile. Thorough investigation, however, meets with the

TABLE IIIA.—RATIO OF CONCENTRATION

	Liver bile	Gall bladder bile	Ratio of concentration
Hydrogen-ion concentration	6.71	5.96	....
Carbon dioxide	95.5	20.5	0.21
Chlorine, mgm. per cent	243.6	79.8	0.32
Bile acid, mgm. per cent	204.5	719.5	3.6
Phosphorus, mgm. per cent	27.5	200.9	7.3
Milliequivalent per liter base	187.5	211.2	1.1
Calcium, mgm. per cent	8.8	24.3	2.8
Magnesium, mgm. per cent	Practically none		
Total nitrogen, mgm. per cent	178.4	382.7	2.2
Non-protein nitrogen, mgm. per cent	12.4	43.5	3.5
Protein nitrogen, mgm. per cent.	166.1	399.1	2.0
Solids, gm. per cent	6.6	21.1	3.2

TABLE IIIB



Anions and cations in M eq/L.

greatest difficulties, since we know very little about the quantitative composition of bile. Elaborate chemical studies of the composition of bile by Ravdin have shown wide variations, the studies of which offer but little hope of drawing definite conclusions. Our own similar chemical studies have likewise defied any logical interpretations. The acidification of bile during its concentration in the gall bladder was first recorded by Okada and later confirmed by several authors. The mechanism, however, by which this process takes place, has never been clearly demonstrated.

We therefore attempted to make parallel analyses of both liver and gall-bladder bile in dogs, estimating the main factors which affect the acid-base equilibrium. Since a number of experiments indicated that different anesthetics and drugs affect the quality of the bile, special precautions were taken in obtaining the bile.

First, we performed a laminectomy in the middorsal region under local anesthesia and transected the spinal cord. About 1 hour later when the dog had recovered from the shock, the abdomen was opened, the cystic duct clamped, and a glass cannula inserted into the common duct. This cannula was connected with a rubber tube leading to a glass container in which the bile was collected under oil. The carbon dioxide and hydrogen-ion concentration values were determined immediately.

Standard methods for blood and urine were used for the bile analyses, which were rendered difficult because of the mucus and color content. Tables IIIA and IIIB show the average results of the analyses of 7 liver and 12 gall-bladder biles of other dogs electrocuted. It is obvious from the study of these charts that our analyses as well as those of previous workers fail to explain entirely the acidification of the bile in the gall bladder. It is quite surprising to note that in spite of the acidification there is a rapid absorption of calcium and carbon dioxide ions. The only acid which seems to increase to any extent is the phosphate and even this, as is shown on the table, accounts for only part of the change. The × anion of Ravdin remains a mystery.

NITROGEN CONTENT OF THE BILE OF NORMAL AND DISEASED GALL BLADDERS

Since the total nitrogen in bile seems to maintain a fairly constant level, deviations from this level might be of importance for understanding the pathology of this organ. Pathological processes in the gall-bladder wall might merely be associated with changes in nitrogen content of the bile, or these changes might be the primary cause for gall-bladder reactions.

Little work has been done on the nitrogen content of bile. Gunderman found that the

nitrogen content in stone-containing gall bladders was variable, while it was usually higher in cholecystitis. Boekelman arrived at similar conclusions by aspirating bile from the duodenum in man.

We conducted a series of observations to confirm those conclusions.

First, we examined 41 human gall bladders obtained at postmortem. We tried to make a gross diagnosis of the gall bladders in each instance, using as a basis only the most obvious signs, which were little influenced by postmortem changes. The diagnoses of stones, adhesions, hypertrophy of the wall and obliteration of the cavity could be made with assurance, but we did not try to make any finer diagnoses, or to conduct microscopic examinations in this series, since postmortem changes do not permit such precise study.

In our second series, which consisted of 13 fresh specimens obtained at human operations, a more definite pathological diagnosis was made. This was confirmed by the clinical history of the patient and by microscopic examination. Fresh bile was available in this series for chemical studies. For the sake of comparison the same classification was applied here as in the postmortem series, the similarity in the results showing that postmortem changes had not influenced the figures of the postmortem bile to a great extent.

In addition, determinations of the protein phosphorus were made, using the colorimetric method of Fiske and Subbarow.

A glance at Tables IV and V shows that no definite correlation exists between the nitrogen and phosphorus content of bile and diseases of the gall bladder. While there is no marked difference in the average figures in stone-containing, normal and chronically diseased gall bladders, there is a great variation in the individual figures of each group. Total nitrogen, for instance, in the group with chronic changes varies from 55 to 924 milligrams per cent.

Animal experimentation yielded similar results. We found in dogs, where the common duct was ligated, that the total nitrogen rose in some cases, while it fell in others. The average figure in 8 normal dogs was 340 milligrams per cent.

PROTEIN INJECTION INTO THE GALL BLADDER

We learn from the last series of experiments that no conclusions can be drawn about the pathology of the gall bladder from the nitrogen content of bile.

However, there still remains the question as to whether increase in the nitrogen content can set up a reaction in the gall-bladder wall.

We tried to approach the matter experimentally by increasing the nitrogen content and observing the effects. This was done by the rough method of injecting egg albumen into the dog's gall bladder. Six cubic centimeters of undiluted white of egg or 6 cubic centimeters of a 6 per cent solution of crystalline purified egg albumen in Ringer's solution were injected into the gall-bladder cavity of the dog either by means of needle puncture or with the catheter technique. In some experiments the material was injected into the wall of the gall bladder at 6 or 8 different points. Where the material was introduced into the gall-bladder cavity, the gall bladder was usually allowed to remain patent, but in some instances the common or cystic duct was ligated.

Fifteen dogs were operated upon, none of which died or showed clinical signs of severe illness as a result of the injections. However, when the dogs were electrocuted 48 hours after the operation, 13 of the 15 gall bladders showed active recent inflammation. No difference in reaction was found regardless of which technique had been used.

The reaction was characterized by edema, hemorrhage, and a fibrinous exudate. Histologically the most constant finding was edematous thickening of the serosa with round cell infiltration and dilatation of the lymphatics. Fibrinous deposits over the serosa were a frequent finding.

We can rule out traumatization as a cause for this reaction since the same results were obtained on the free surface of the gall bladder when the injection was made through the liver surface or when the material had been introduced through a catheter.

We can say in summary that egg albumen, introduced into the wall or cavity of the dog's gall bladder by various techniques, almost regularly sets up a reaction in the gall-bladder wall.

THE TOXIC EFFECT OF BILE

Having obtained marked reactions in the gall bladder of dogs after the injection of foreign protein, the next procedure in our studies was to examine the constituents of bile itself for any possible toxic effect.

Bile as a whole cannot be considered toxic to the gall-bladder wall if present in normal concentration. As seen from our control experiments, removal of bile from a dog's gall bladder by means of a catheter and replacing it by bile from another dog leaves the gall-bladder wall unchanged. Similarly ox bile introduced into the dog's gall bladder gives negative results.

It has long been known, however, that bile has a marked toxic effect outside of the gall bladder, a subject upon which a large amount of literature has been written. The local destructive power of bile in contact with living tissue has been demonstrated repeatedly. Flexner, and Meltzer and Salant showed that bile causes necrosis of living cells and hemolysis of blood cells. Pancreatic necrosis has been produced by many authors with gall-bladder bile. Dragstedt (17) demonstrated an acute necrosis of the pancreas which had been brought in contact with bile through a window in the gall-bladder wall. Necrosis of muscle and subcutaneous tissue results from the injection of sterile bile or a solution of bile salts, as demonstrated by Andrews in the experimental animal. Similarly, lesions in the stomach wall and in the salivary glands have been produced by Sellards.

Flexner demonstrated that it is bile salts which constitute the toxic element in bile, and expressed the opinion that gall-bladder bile, in which bile salts are relatively concentrated, is more toxic than liver bile.

In addition to the local toxic effect, there is a well known systemic toxic action of bile. Many investigators have found that animals die within a short period of time from intravenous injection of bile or bile salts. Dragstedt (18) demonstrated that animals died within 2 or 3 days when the common bile duct was anastomosed to the vena cava or portal vein. In discussing the toxic action of bile and bile salts, we ought to mention briefly a mechanism which is supposed to compensate

TABLE IV.—NITROGEN CONTENT OF BILE*

	No.	mgm. Total N	Average	Prot. N	Average	NPN	Average	Prot. P	Average
Stone containing	1	426.0		150.0				13.2	
	2	315.0		150.0		162.0			
	3	577.0	496.2	170.5	118.2	375.0	326.5	34.4	20.3
	4	577.0		93.8		442.5		13.8	
	5	498.0		114.0		330.0			
Chronic changes on the gall-bladder wall (adhesions, hypertrophy, obliteration, etc.)	6			48.6		37.4		11.8	
	7			75.0		70.0			
	8	55.0		45.0				10.0	
	9			120.0				31.4	
	10	353.0		120.0				20.0	
	11	543.0		384.0				20.0	
	12	555.0		329.0				36.2	
	13	924.0		462.0		444.0		37.0	
	14	200.0		40.0		143.0		12.2	
	15	387.0		166.5		199.5		24.6	
	16	273.0	429	78.2	174.9	207.0	167.7	25.6	21.3
	17	666.0		366.0		285.0		28.4	
	18	327.0		130.5		171.0		13.3	
	19	568.0		250.5		250.5		25.0	
	20	498.7		156.5		313.0		20.0	
	21	375.0		156.5		221.3		18.6	
	22	354.0		125.2		222.0		21.3	
	23	354.0		136.0		180.0		9.5	
	24	480.0		181.5		300.0		16.9	
	25	300.0		115.5		177.0		20.6	
	26	510.0		187.0		300.0		25.0	
Normal and distended gall bladder	27	62.0		43.1		12.3		11.4	
	28	770.0		375.0				47.0	
	29	476.0		125.0				16.1	
	30	706.0		300.0				13.2	
	31	750.0		240.0				12.9	
	32	266.0		94.0		166.0		20.0	
	33	300.0		199.5		78.0		26.6	
	34	555.0	441	250.0	168.3	300.0	152.8	27.8	21.6
	35	240.0		65.2		177.0		15.4	
	36	177.0		49.8		123.0		11.8	
	37	354.0		81.7		273.0		12.5	
	38	261.0		93.7		125.0		19.0	
	39	798.0		177.0		600.0		23.1	
	40	600.0		354.0		231.0		48.4	
	41	300.0		77.0		207.0		19.0	

*Material obtained at postmortem—41 human postmortem biles.

TABLE V.—NITROGEN CONTENT OF BILE*

	No.	Mgm. % total nitrogen	Mgm. % protein nitrogen	Mgm. % non protein nitrogen
Gall-bladder bile	1		521.4	
Stone-containing bile	2		28.0	
Acute change (round cell infiltration, edema, etc.)	3	24	10.7	
	4	207	111.0	88.0
	5		37.5	
	6	75	34.1	41.6
Chronic change (hypertrophic processes, fibrous thickening, etc.)	7		practically none	
	8	285	136.5	125.2
	9	251	115.0	125.0
	10	222	30.0	
About normal (very little cell reaction) distended gall bladder	11	157	55.0	
	12	414	222.0	157.0
Liver bile	13	44	12.0	28.0

*Material obtained at operation—13 human operation biles.

for this toxic effect and which is said to be present in bile proteins.

In a study of the hemolytic action of bile *in vitro*, Bayer found that serum protein exerts an inhibitory effect on this process while egg albumen has no such effect. These observations were controlled and confirmed by Sellards who demonstrated that these protective elements were present in serum even in high dilutions. Sellards as well as many other investigators claimed that this protective action of serum against the toxicity of bile plays an important part in acute hemorrhagic pancreatitis. This hemorrhage, often found in necrosis of the pancreas, presumably tends to neutralize the action of the bile.

Similar protective action was attributed to mucus and other colloidal substances present in bile itself by Flexner, who assumed that bile protein diminishes the toxic action of bile, if brought in contact with pancreatic tissue.

TOXIC EFFECT OF BILE IN THE GALL-BLADDER WALL

It has been suggested recently by Andrews that bile may, under certain circumstances, acquire a destructive power in the gall-bladder wall, in a manner similar to gastric juice in the stomach and pancreatic juice in the pancreas. The most obvious constituent of bile which has a toxic and destructive effect on body tissues, is the bile salts, which are present in gall-bladder bile in rather high concentrations. Figures of 7 or 8 per cent are frequently found while the textbooks of Hawk and Hammersten give the normal concentration at about 10 per cent.

Whatever the normal concentration of bile salts in bile is, we attempted experimentally to increase the bile salt concentration in bile and to observe the effects of this on the gall-bladder wall. The results were striking, inasmuch as the reactions obtained in the gall-bladder wall resembled human cholecystitis more closely than any reaction ever obtained previously.

Two forms of bile salts were used, commercial bile salts[1], and the same material freed by alcohol extraction from the large percentage of non-alcohol-soluble substances which it contains. The injections were all made by means of the non-traumatizing technique.

The result of these injections was the production of acute cholecystitis with all the features of human cholecystitis. There was marked enlargement of the gall bladder with the cystic duct obviously shut by swelling of the mucous membrane. The color of the gall bladder was either grayish-white or reddish, the serosa being covered with thick fibrinous membranes, which in many instances caused the adjacent viscera to adhere to the gall bladder. The gall-bladder wall was thickened up to 7 or 8 millimeters and was rigid in character. On microscopic examination the reaction was most marked in the serosa, which was 8 to 10 times its normal thickness and moderately infiltrated with round cells. There were marked hyperemia and punctate hemorrhages, along with dilatation of the lymphatics.

A fibrinous exudate was found on the serosa and a slight leucocytic infiltration in certain places. The muscularis was moderately edematous and contained a considerable number of large and small mononuclear cells, with very few polymorphonuclear leucocytes. The mucosa in most instances was practically normal.

The reactions obtained with purified bile

[1]Armour & Co.

salts were somewhat stronger than those with commercial bile salts, suggesting that the protein of the latter preparation had exerted a slight protective action against the toxicity. This possible protective action of bile protein will be discussed in more detail in later experiments.

To elucidate still further the toxic action of bile salts, we conducted a more thorough investigation by making use of different bile salt fractions.

Table VI shows the results obtained from the injections in 71 experiments.

For the sake of comparison the 16 experiments using commercial and purified bile salts discussed, have been included in this table. The groups are arranged in the order of dedecreasing toxicity.

We find that the bile salt mixtures are not the most effective preparations, but that the most severe reactions are obtained with isolated fractions, as desoxycholic, apocholic, and cholic acid which often cause gangrene of the gall bladder and death of the animal. Sodium desoxycholate proved to be the most powerful fraction and in a concentration as low as 7.5 per cent gave a marked reaction. Positive results were obtained with 7 per cent apocholic acid, while higher concentrations were necessary to produce similar changes with cholic acid.

Severe cholecystitis resulted from the injection of concentrated dog bile, which was obtained by evaporation of dog bile by means of a fan to about ⅓ of its volume and which is known to contain mainly taurocholic acid.

The effectiveness of bile salts is increased rather than decreased by the process of hydrolysis, which consists of alcohol precipitation of the bile salts, sodium hydroxide extraction, precipitation with hydrochloric acid and finally dissolving them with alcohol and sodium hydroxide. We obtained marked reactions with an 8.7 per cent solution and very severe changes, often accompanied by death, with a 20 per cent solution.

Glycocholic acid, on the other hand, proved to be much less effective and produced changes in the gall-bladder wall only in higher concentrations. A study of decholin (dehydrocholic acid) which is used in the medical management of human cholecystitis, was added for the sake of completeness. No appreciable reaction is obtained with any concentration.

TABLE VI.—RELATIVE TOXICITY OF DIFFERENT BILE SALTS

Fraction and concentration used	Number of experiments	Final concentration in gall bladder %	Reaction
1. Desoxycholic acid 8 to 13%	13	7.5 to 12	Severe reaction. Gangrene of gall bladder, bile peritonitis, and death
2. Apocholic and cholic acid 7 to 12%	17	7.4 to 11.2	Same
3. Concentrated dog bile (mostly taurocholic acid)	4		Severe cholecystitis, bile peritonitis, and death
4. Hydrolyzed bile salts 10 to 20%	6	8.75 to 20	Severe cholecystitis and death
5. Purified bile salts 10 to 20%	4	8.7 to 18	Same
6. Commercial bile salts 10 to 20%	12	8.5 to 20	No death. Bile peritonitis and cholecystitis
7. Glycocholic acid 8 to 13%	9	7.5 to 11.1	Cholecystitis—occasionally on high concentration, mostly normal gall bladder
8. Decholin (dehydrocholic acid) 20%	6	9.4 to 15	Normal gall bladder

The final concentration of bile salts in the gall bladder in each experiment was calculated in the following manner:

The size of the gall bladder was estimated according to the weight of the dog and the gall bladder in the starving dog considered to be nearly well filled with bile. The bile salt concentration of normal gall-bladder bile in the dog was thought to be 7.5 per cent.

The gross and microscopic changes in most of these gall bladders are similar to those described in the commercial bile salt group. We might add the frequent occurrence of bile peritonitis, the pathogenesis of which is still only little understood. Bile peritonitis, either localized around the gall bladder or in a diffuse form was often seen without visible perforation of the gall bladder or bile ducts.

No qualitative differences were found in the appearance of the gall bladders after injection of the various fractions, the only differences being quantitative, with the exception of the desoxycholic group. In these cases apparently all of the layers were involved, leucocytic infiltration and hyperemia being found in the mucous membrane and the muscular layer as well as in the serosa. Whether this was due to a direct action of the desoxycholic acid on

the mucous membrane or to secondary involvement of the inner layers from the serosa, cannot be determined from the anatomical picture.

IS BILE PROTEIN PROTECTIVE AGAINST THE TOXIC ACTION OF BILE SALTS?

Protein is said to have an inhibitory influence on the toxic action of bile salts, as aforementioned.

In relation to our present work, it is of special interest to determine whether such a protective mechanism is actually present in the mucus and protein of bile, as claimed by Flexner and others. If this theory is correct, bile, deprived of its protein, is thus converted into a toxic substance.

In regard to this point the following set of experiments was carried out:

Ox or dog bile was deproteinized either by boiling for 5 minutes and filtering or else by autoclaving for 15 minutes at 15 pounds and filtering. This was then injected into a dog's gall bladder in 13 experiments. In 9 instances in which this bile had been introduced by means of the catheter cannula technique, normal or practically normal gall bladders were obtained. Two of 4 cases, however, in which the material had been introduced by means of needle puncture and followed by duct ligation, showed a severe reaction, apparently due to the duct ligation. We might thus conclude that removal of the protein does not convert bile into a toxic substance.

STUDY OF THE TOXIC EFFECT OF BILE SALTS

From the previous studies it is seen that normal bile, which has a toxic action on tissues outside of the gall bladder, is not toxic for the gall-bladder wall itself, if present in normal concentration, even if it is deprived of its protein. An increase in concentration, however, converts the bile into a substance which is highly toxic to the gall-bladder wall.

At this point we might inquire as to what extent bile has to be concentrated to bring about this reaction.

Possible means of concentrating the bile are as follows: (1) adding bile salts to whole gall-bladder bile; (2) concentrating the dog's own bile within the gall bladder; (3) replacing the gall-bladder bile with another animal's bile which has been concentrated previous to the introduction.

The first method has been widely applied in studying the relative toxicity of various bile salt fractions. It is less useful for a quantitative analysis of the toxic action, in so far as the degree of concentration in the gall bladder to which the bile salts have been added is an unknown factor.

The concentration of the dog's own bile, without removal from the gall bladder, would be the ideal method. However, such attempts have met with great difficulties. Since all water-absorbing chemicals damage the gall-bladder wall severely, we tried to accomplish this concentration by washing the gall-bladder bile with dry, warm air for a certain length of time. Increase in the concentration of solids accompanied by a slight reaction in the gall-bladder wall, was obtained in some instances. However, the number of positive results and the degree of reactions obtained are too small from which to draw any conclusions.

More satisfactory results were obtained from the third method mentioned, namely, the replacement of gall-bladder bile by bile concentrated previous to its introduction. Since the gall bladder was emptied before we introduced the known material, we excluded fairly well unknown factors in the analysis.

The bile, used for the experiments, was concentrated in the following manner:

Dishes, each containing 200 cubic centimeters of fresh ox bile, were exposed to an electrical fan for varying periods of time, allowing evaporation and concentration down to 150, 110, 88, and 60 cubic centimeters. These different biles were injected by the catheter method into the dog's gall bladder, which was emptied previously by aspirating the entire bile content.

Table VII gives the results of these experiments and needs little additional comment. Concentration of ox bile to about half its volume has marked local and systemic effects in the dog while death frequently occurs from stronger concentrations.

To prove that the changes obtained were actually due to the toxic action of concentrated bile and not to accompanying bacterial

TABLE VII.—EFFECT OF VARIOUS CONCENTRATIONS OF OX BILE ON DOG'S GALL BLADDER

Ox bile	No. of experiments	Results
Plain	3	Gall bladder practically normal in all instances
Concentrated 150	5	Gall bladder normal in 2 cases, slight reaction in 3 cases
Concentrated 110	6	Moderate degree of cholecystitis, 2 cases; moderate degree of cholecystitis plus bile peritonitis, 2 cases; severe cholecystitis, 2 cases
Concentrated 88	6	Severe cholecystitis, 1 case; severe cholecystitis plus bile peritonitis, 1 case; death and severe reaction, 4 cases
Concentrated 60	4	Severe cholecystitis, 1 case; severe cholecystitis plus bile peritonitis, 1 case; death plus severe reaction, 2 cases

TABLE VIII.—CONTROL EXPERIMENTS WITH CONCENTRATED AND REDILUTED OX BILE

Ox bile	No. of experiments	Results
Concentrated 150, rediluted	2	Gall bladder normal
Concentrated 110, rediluted	2	Gall bladder normal
Concentrated 88, rediluted	2	Normal, 1 case; slight reaction, 1 case
Concentrated 60, rediluted	2	Gall bladder normal

infection, the following experiments were undertaken:

Since bacterial cultures revealed that the biles which had been exposed to air for any considerable time contained a great number of bacteria, we rediluted these concentrated biles to their original volumes and injected them into the dog's gall bladder.

No reaction was obtained, as seen from Table VIII, which proves that bacterial infection is not the cause of the changes obtained in the gall bladders.

EFFECT OF VARYING HYDROGEN-ION CONCENTRATION ON THE TOXICITY OF BILE SALTS FOR THE NORMAL GALL BLADDER

In subjecting the preceding findings to thorough criticism, there is still the possibility that the reactions produced might have been due to a change in the hydrogen-ion concentration of gall bladder bile. This change in hydrogen-ion concentration might convert the bile into a toxic substance. There are 2 ways of controlling this factor.

One method would be to produce a change in the hydrogen-ion concentration of gall bladder bile in the experimental animal by adding acid or alkali and observing the effect. The other method consists of the introduction of bile salt solution previously adjusted to the hydrogen-ion concentration of gall-bladder bile. Both methods have been applied.

The first method clearly demonstrates the marked buffering action of bile. Injection of 5 cubic centimeters of glacial acetic acid into the dog's gall bladder was followed by total gangrene of the gall bladder and death of the animal. The hydrogen-ion concentration after adding this acid to the gall-bladder bile and thoroughly mixing, was about 2. Similarly, total gangrene of the gall bladder resulted from adding 10 cubic centimeters of 20 per cent sodium carbonate to the gall-bladder bile with a final hydrogen-ion concentration of 10.

More detailed information concerning the buffering potentialities of bile is yielded from the following experiments:

After aspiration of the total gall-bladder bile, the gall bladder was washed with a citric-phosphate buffer solution and was left filled with this solution. When the animals were electrocuted 48 hours later no changes in the gall-bladder wall were found. In other experiments, the same procedure was performed, a citric-phosphate solution of hydrogen-ion concentration of 3 being used. In one of these cases the gall bladder, containing a thin colorless fluid, showed a moderate degree of acute cholecystitis, but in the other it was refilled with dark bile and revealed a normal wall. It is obvious that the bile, which had re-entered the gall bladder through the hepatic ducts, by its buffering action, had kept the acid mixture from developing an irritating action on the wall of the gall bladder.

Various difficulties were encountered in performing the second series of experiments, namely, the introduction into the gall bladder of bile salts previously adjusted to the hydrogen-ion concentration of gall-bladder bile. In the first place, bile salts are easily pre-

TABLE IX.—EFFECT OF VARYING HYDROGEN-ION CONCENTRATION ON TOXIC EFFECT OF BILE SALTS ON THE NORMAL GALL BLADDER

Injected solution	Hydrogen-ion concentration	Result
1. Sodium desoxycholate 12,5%	pH after adjust. with 0,1 mol. citr. acid: 7,3	Severe cholecystitis
2. Sodium desoxycholate 9 %	7,2	Severe cholecystitis
3. Cholic acid 12,6%	7,8	Medium cholecystitis
4. Cholic acid 8 %	7,4	Medium cholecystitis
5. Purified bile salts 15 %	pH without adjust. 5,7	Moderate cholecystitis
6. Purified bile salts 15 %	5,7	Moderate cholecystitis
7. Citric acid-NaOH	1 M. citric acid adjust. with NaOH 10% 7	Normal gall bladder
8. Citric acid-NaOH	7,4	Normal gall bladder

cipitated by adding acid to a bile salt solution. Furthermore, we have to consider that many acids, if brought in contact with the gall-bladder wall, themselves set up a reaction. We were able to overcome these difficulties by the use of a weak citric acid solution, which, as seen from controls, would not cause any change in the gall-bladder wall even in a concentration higher than that used. As an example, the adjusting procedure for sodium desoxycholate is given as follows: 12 grams of sodium desoxycholate are dissolved in 100 cubic centimeters of distilled water. This solution, which has a hydrogen-ion concentration of 8.4, is heated to body temperature and 0.1 mol. citric acid added one drop at a time. The precipitate which occurs is dissolved by shaking. After approximately the desired hydrogen-ion concentration is reached (determined first roughly by a set of indicators) more exact determination is done with Hastings' colorimeter. Table IX shows the results of experiments with adjusted bile salts, and the controls with citric acid. It is seen that the toxic effect of bile salts on the gall-bladder wall is not changed when the hydrogen-ion concentration is adjusted to that of gall-bladder bile previous to injection. Citric acid solution, furthermore, in concentrations even higher than that used for the adjustment, does not in itself affect the gall-bladder wall.

ALLERGIC GALL-BLADDER REACTION

It is suggested by clinical observations that a reaction may occur in the biliary system in man which is based on an anaphylactoid condition. Many surgeons have seen flare-ups of old gall-bladder disease apparently due to an anaphylactic response against certain foodstuffs, such as chicken, egg, milk, cheese, etc., omission of these foods affording relief. Alvarez and more recently Croutch reported several cases of this kind. The anaphylactic nature of this process, however, has only been suspected and no experimental proof has ever been given.

Hence the following experimental observations may be in place:

Each of 3 dogs received intravenous injections of crystallized egg albumen within a period of 3 days, each injection consisting of 5 cubic centimeters of a 6 per cent solution. No reactions were observed either during or after these injections. After an interval of 6 days, similar injections of a 6 per cent solution of the same material were made, but this time in much larger quantities, sufficient to produce visible toxic symptoms. In 2 of the animals the reaction consisted of vomiting, trembling, irregular respiration, and passage of feces, while in the third the response was much more pronounced, consisting of vomiting, loss of consciousness, cessation of respiration for 3 minutes and generalized convulsions. The quantity of the last injection was 15 to 20 cubic centimeters in the first 2 dogs and 25 cubic centimeters in the third. The animals were electrocuted ½ hour following the last injection and postmortem examinations were made immediately. In all 3 cases there was found marked edema of the gall-bladder wall, most marked in the serosa. Microscopic examination of the liver showed markedly constricted arterioles.

As a control, egg albumen was injected in large amounts into 3 other dogs, which had not received any previous injections. In 2 of these animals no symptoms were visible until 40 cubic centimeters had been injected. After 45 cubic centimeters however, the reaction was marked but consisted only of vomiting and passage of feces. In the third dog these symptoms did not appear until 60 cubic centi-

meters had been injected. Postmortem examination after electrocution revealed perfectly normal gall bladders.

A comparison of the results in the 2 series of animals suggests the conclusion that the reaction obtained after the last injection in the first series was an anaphylactic response, since it required much less albumen to produce a response in the previously sensitized dogs than in the control animals. Furthermore, the constriction of the arterioles in the liver in the first series of animals is suggestive of anaphylactic change.

BILE SALT INTRAVENOUS INJECTIONS

It is of great interest for the understanding of gall-bladder symptoms in man that it is possible to produce a condition of anaphylaxis experimentally.

Such an allergy might explain the gall-bladder symptoms which occur after the intake of certain foods. When we consider the frequency of gall-bladder disease, however, as contrasted to the comparatively rare observation of food allergy, we are inclined to believe that allergy, caused by exogenous food substances, is not of great practical importance.

Many possibilities present themselves, however, when we consider endogenous body substances. Many metabolic products may serve as sources of allergic states as well as any disturbance in the detoxifying action of the liver cells.

This consideration becomes of much more practical importance in view of experimental results which we obtained.

Having seen the powerful toxic action of bile salts in the gall-bladder wall, at a concentration which exceeds only slightly the normal values, we were tempted to suspect that an anaphylactic mechanism might be responsible for these effects.

The results which we obtained are striking, but since these studies are not as yet completed, we are not reporting the detailed work. We do not obtain positive results with such regularity that we can predict the conditions under which they will occur. There are still many factors the nature of which are unknown to us.

There follows a rough outline of the experiments:

Intravenous injections of commercial bile salts, purified bile salts or sodium desoxycholate were given to 26 dogs, concentrations of 5 or 10 per cent being used.

The number of injections given to each animal as well as the total amount injected varied considerably in the different experiments.

In one series we gave single injections, which we discontinued after toxic symptoms, such as vomiting, convulsions, etc., became visible. This stage was reached in our animals which had an average weight of 5 to 6 kilograms after 25 to 30 cubic centimeters of the 5 per cent solution had been injected. Those animals which did not die spontaneously, were electrocuted a few minutes after the injection.

Another group of dogs received 2 injections each, 20 minutes apart. We carefully avoided getting a marked toxic effect from the first injection, while the amount administered in the second injection was large enough to produce visible toxic signs or death of the animal.

A third group received 4 to 5 injections at hourly intervals, beginning with a comparatively small amount (10 to 12 c.cm.) in the first injection and ending with 15 to 40 cubic centimeters in the last one. The last group received daily injections for about a week, and these animals were killed a few days after the last injection.

These experiments resulted in marked reaction of the gall-bladder wall in more than half of the cases, the positive results being found in the first 3 groups, while the fourth was completely negative.

No definite correlation, however, can be made between the different methods of administering the bile salts in the different groups and the reactions obtained. The number of positive results was greater in the first and second groups, where the 1 or 2 injections had been given within 3 to 20 minutes, than it was in the third. In the latter group the injections had extended over several hours.

The shortest time in which a reaction occurred was 3 minutes. Purified bile salts

seem to be more effective than any other fractions.

Postmortem examination revealed a grayish-white gall bladder with congestion of the serosa. Edema, most marked on the liver surface, was a prominent feature. No changes were found anywhere else in the body. Microscopic examination showed the serosa to be edematous, and swollen to 6 times its normal thickness.

EVALUATION OF STUDY

The gall bladder contains the strongest solution of any substance which the human body elaborates, and this substance (bile acids) is an exceedingly toxic one. The normal gall bladder is a concentrating mechanism of high potency and our experiments show that only a slight overaction of its every day action may produce a concentration whose effect is damaging to the gall bladder and the surrounding tissues. This effect might be brought about in three different ways: First by the gall bladder itself from simple overaction, or second, by the excretion of bile by the liver which is too concentrated in the first place, or third, by the excretion of bile by the liver which contains substances which might become toxic on further concentration.

The first of these theories seems the least probable. The range of the normal liver bile in bile acid content is a wide one. The amounts may be very small, but the gall bladder seems to tend to absorb water and to concentrate them all to about the same level. It has been shown in previous communications that the normal gall bladder in the course of its concentrating action absorbs but little bile salts during the period between emptyings, but that if the action is prolonged, by stasis, eventually all the bile salts will be absorbed. Such an action has been shown to be capable of precipitating the cholesterol in the bile which needs the bile salts to hold them in solution. This process apparently takes place without the patient going through an attack of cholecystitis, as the many specimens of such gall bladders show, taken from individuals who have never had such an attack.

The second alternative, an increased secretion from the liver, also seems improbable, as if such were the case values within the toxic range would certainly have been reported previously by some of the many who have worked in this field.

The third theory, a qualitative difference in the bile salts excreted by the liver, cannot be so easily disposed of. Our experiments indicate a far higher degree of toxicity for some of the unconjugated bile acids. We have previously reported the findings of large amounts of such bile acids in the liver bile of a diabetic, and it seems not unlikely that such may not be an uncommon occurrence. The present limitations of bile salt chemistry make it impossible to recognize even large amounts of such materials in the amount of bile recoverable from a gall bladder, but one may hope that progress in this field may soon make such analyses possible.

If some such theory of the origin of some cases of gall-bladder disease is entertained, it fits in well with many of the observed facts, which are thought by some to militate against bacterial theories. The frequent afebrile cases, failure to grow organisms in many cases, the pathological picture which Denton describes as resembling a hemorrhagic infarct, are all consonant with such a chemical mechanism. The low values from bile acids found in most cases of closed acute gall bladders is explained on the assumption that the original high concentration causes an edema which permits the rapid leaking out of the contents by osmosis. Such can actually be seen in our experiments in the staining of the local peritoneum.

SUMMARY

1. A non-traumatic technique for introducing substances into the dog's gall bladder is described.

2. Most strains of bacteria even when injected in overwhelming numbers do not cause cholecystitis. If trauma is added these same strains do cause cholecystitis.

3. Carbon dioxide and chlorine are absorbed rapidly from the normal gall bladder, while phosphorus is excreted but an unknown anion accounts for much of the acidification.

4. Chemical examination of 41 human postmortem biles and 13 biles obtained at

human operations shows that there is no definite correlation between the nitrogen content of the bile and the changes of the gall-bladder wall, the fluctuations in nitrogen content being extreme in both.

5. Injections of egg albumen into the dog's gall bladder set up an active acute inflammation.

6. Changes of the gall-bladder wall of the dog which on gross and microscopic examination closely resemble those found in human cholecystitis, were produced in 72 experiments by the injection of bile salts. The differences in the activity of different fractions of bile are mainly quantitative in nature. Desoxycholic acid is the most effective fraction, causing gangrene of the gall bladder and death of the animal in many instances, while purified and hydrolyzed bile salts are somewhat weaker. Glycocholic acid causes a marked reaction only in higher concentration.

7. Injection of deproteinized dog or ox bile into the dog's gall bladder leaves the gall-bladder wall unchanged. No protective action of protein, as described in the literature, can be found.

8. A quantitative study of the toxic effect of bile salts was made by replacing gall-bladder bile in the dog by bile concentrated previous to the injection. Bile concentrated to about half its volume proved to have a marked effect.

9. Changes in the hydrogen-ion concentration of bile rarely bring about a reaction in the gall-bladder wall unless they are extreme, less than 3 and greater than 10. Such changes are not likely to arise in man. The toxic effect of bile salts is not due to a change in hydrogen-ion concentration since adjustment of the bile salts to the hydrogen-ion concentration of the gall-bladder bile previous to the introduction, did not diminish their toxic effect.

10. It is possible to produce experimentally an allergic condition in the gall bladder. Intravenous injection of egg albumen caused an edema in the gall-bladder wall of previously sensitized dogs, while no reaction occurred in control animals.

11. A marked edema of the gall-bladder wall was produced by the intravenous injection of bile salts. The shortest time in which this reaction took place was 3 minutes after the injection.

It has been suggested that a temporary increase in bile salt concentration in the gall bladder brings about human cholecystitis.

BIBLIOGRAPHY

1. ALVAREZ, W. C. Proc. Staff Meet., Mayo Clin., 1934, 9: 45.
2. ANDREWS, E. Must we revise our indications for cholecystectomy? Internat. Clin., 1935, vol. 3, series 45.
3. ANDREWS, E., and HENRY, L. D. Bacteriology of normal and diseased gall-bladders. Arch. Int. Med., 1935, 56: 1171.
4. BAYER. Biochem. Ztschr., 1907, 5: 368; 1908, 9: 58.
5. BLACKSTEIN. Bull. Johns Hopkins Hosp., 1891, pp. 96 and 121.
6. BOEKELMAN. Klin. Wchnschr., 1928, 7: 65.
7. BOYD. Textbook of Surgical Pathology.
8. BRAMS, J., and DARNBACHER, L. Radiology, 1929, 13: 103.
9. BROWN, R. O. Arch. Int. Med., 1919, 23: 185.
10. CHIAROLANZA, R. Ztschr. f. Hyg., 1908, 1: 11.
11. CHIARY. Prag. med. Wchnschr., 1893, No. 22; Ztschr. f. Heilk., 1894, 15: 199.
12. CROUTSCH. Personal communication.
13. CUSHING and LIVINGOOD. Johns Hopkins Hosp. Rep., 1900, 9: 543.
14. DARNBACHER, L., and SACKS, J. Radiology, 1931, 17: 538.
15. DENTON, T. Arch. Surg., 1927, 14: 1.
16. DOERR. Zentralbl. f. Bakteriol., 1905, 39: 624.
17. DRAGSTEDT, LESTER R. Pathogenesis of acute pancreatitis. Arch. Surg., 1934, 28: 232–291.
18. DRAGSTEDT, LESTER R., and SPURRIER, BERT. Effect of diversion of bile into vena cava and portal vein in dogs. Proc. Soc. Exper. Biol. & Med., 1929, 26: 303.
19. DRENNAN, T. G. Ann. Surg., 1922, 76: 482.
20. EMMERICH and WAGNER. Zentralbl. f. allg. Path. u path. Anat., 1916, 27: 433.
21. FEINBLATT, H. M. New England Med., 1928, 199: 1073.
22. FLEXNER, SIMON. The constituent of the bile causing pancreatitis and the effect of colloids upon its action. J. Exper. Med., 1906, 8: 167.
23. GILBERT and DOMINICI. Compt.rend. Soc. de biol., 1893, Jan. 20, p. 38.
24. GILBERT and GIRODE. Compt.rend. Soc. de biol., Par., 1890, p. 756; 1893, p. 956.
25. GRAHAM. Diseases of the Gall-bladder and Bile-ducts. Philadelphia: Lea & Febiger, 1928, 114.
26. GUNDERMAN, W. Mitt. a.d. Grenzgeb. d. Med. u. Chir., 1926, 39: 353.
27. HAMMERSTEN, O. Textbook of Physiological Chemistry.
28. HAWK. Practical Physiological Chemistry.
29. HENKE and LUBARSCH. Handbuch der speziellen pathologische Anatomie und Histologie.
30. HOSPERS, C. A. Arch. Path., 1932, 14: 66–78.
31. HUNLEMUELLER. Klin. Wchnschr., 1924, 3: 349.
32. HUNTER, JOHN. Cited in Rolleston: Diseases of Liver, Gall-bladder and Bile Ducts.
33. ITALIA, F. E. Policlin., 1901: cited Zentralbl. f. Chir., 1901, 28: 693.
34. KOCH, T. Ztschr. f. Hyg. 1908, 1: 1.

35. MAGNER, W., and HUTCHESON, G. M. Cholecystitis. Canadian M. Ass. J., 1932, 27: 469.
36. MANN. The production by chemical means of a specific cholecystitis. Ann. Surg., 1921, 73: 54.
37. MELTZER, S. J., and SALANT, WILLIAM. Studies on the toxicity of bile. J. Exper. Med., 1906, 8: 127.
38. MEYER, K. F., NELSON, N. M., and FENSIER, M. L. J. Infect. Dis., 1921, 28: 457.
39. MOYNIHAN, A. Disease of the gall-bladder requiring cholecystectomy. Ann. Surg., 1909, 50: 1265.
40. NICHOLS, H. T. J. Exper. Med., 1916, 24: 497.
41. OKADA, S. J. Physiol., 1915, 1: 114.
42. OSLER, WILLIAM. Practice of Medicine, 1905. Modern Medicine. Philadelphia: Lea & Febiger, 1907.
43. PEYTON, ROUS, and MCMASTER. Concentrating activity of gall-bladder. J. Exper. Med., 1921, 34: 47.
44. RAVDIN, J. S., JOHNSTON, C. G., RIEGEL, C., and WRIGHT, S. L. Anion-cation content of hepatic and gall-bladder bile. Am. J. Physiol., 1932, 100: 317.
45. REHFUSS, M. E., and NELSON, G. M. Problem of infection in gall-bladder disease, etc. Am. J. Digest. Dis., 1935, 1: 759.
46. ROLLESTON. Diseases of the Liver and Bile-ducts, 1905 and 1929.
47. ROSENOW, E. C. J. Am. M. Ass., 1914, 63: 1835; J. Infect. Dis., 1916, 19: 527.
48. SCHOEBL, OTTO. Experimental cholera carriers. J. Infect. Dis., 1916, 18: 307.
49. SELLARDS, A. W. The hemolytic action of bile and its inhibition by blood serum. Bull. Johns Hopkins Hosp., 1908, 19: 268. Ulceration of the stomach and necrosis of salivary glands resulting from experimental injection of bile salts. Arch. Int. Med., 1909, 4: 502.
50. SHERRINGTON, T. Pathology and Bacteriology. 1892–93, 1: 259.
51. VENEMA, T. A. Berl. klin. Wchnschr., 1917, 815.
52. WILKIE, A. L. Brit. J. Surg., 1927–28, 15.

CARCINOMA OF THE RECTUM

A Plea for Group Study and Treatment

PAUL C. MORTON, M.D., F.A.C.S., New York, New York

THIS analysis comprises all the cases of carcinoma of the rectum at St. Luke's Hospital, New York City, between the years 1924 and 1935 inclusive; both private and ward patients operated upon only by members of the hospital staff are included. It is important to understand early in the discussion that a comparison of these statistics with those of group clinics and clinics headed by one individual doing the great majority of work is of doubtful value. The reason for this statement will be made later. The general purpose of this paper is to present:

1. An analysis of these cases, with special reference to (a) the number of cases seen, divided into operable for cure cases, and inoperable cases; (b) a division of the operable for cure cases into groups in relation to their follow-up records.

2. A general discussion of the diagnosis, and of the pre-operative and postoperative management of cancer of the rectum, and suggestions for improving the care and the end-results, in general hospitals organized as St. Luke's Hospital.

Classification of these patients as to sex, age, pre-operative length of symptoms, and etiology, will not be given in this paper. This information, while available, corresponds in general to that given in all the recent papers. We have no hitherto unknown methods of diagnosis or new technique to offer. Our experience in very recent years has given us a better understanding of the management of these cases, and the adoption of those methods used in other clinics to shorten the length of operation, to protect the patient against peritonitis, and to improve the operative technique, has met with varying degrees of success.

Read before the New York Surgical Society, New York Academy of Medicine, New York City, January 27, 1937.

DIAGNOSIS

Early diagnosis in this condition is the great hope for better therapeutic results. We believe in almost all cases of carcinoma of the anus, rectum, and rectosigmoid, that a proper digital examination will reveal the presence of the growth; this includes an examination, often with the patient in the stooping position and while they are bearing down. The great hope for the early diagnosis of this condition lies in periodic health examinations, including a digital and proctoscopic examination. The general use of the proctoscope will do much to improve the diagnosis and treatment of all rectal conditions. It is a simple procedure, given the proper instruments, a convenient arrangement, and gentleness on part of examiner. A proctoscopic examination should be part of every x-ray examination of the colon.

The question often arises as to how long a growth has been present. We have seen recently, and not included in this group, one patient who was proctoscoped by a competent observer 1 year prior to his admission, with a negative result. A well developed carcinoma within 2 inches of the anus was found at the end of this time.

Biopsy furnishes an accurate diagnosis as to the presence or absence of cancer, with minor exceptions, and should be done wherever possible. A negative diagnosis, however, must be judged together with the clinical findings. Included in this group is the case illustrated of an adenoma of the rectum, but with carcinomatous degeneration in one portion of the growth. Repeated biopsies failed to show carcinoma. Radical resection was performed. The converse is true, and inflammatory lesions, such as chronic ulcerative colitis and amebic dysentery, can be confusing. Every hard, friable, bleeding mass felt with the finger should not be called carcinoma without further examination.

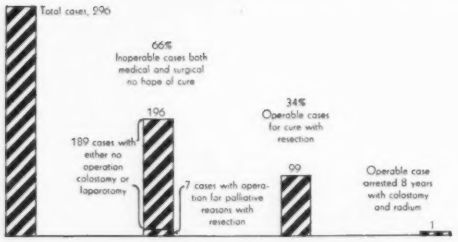

Total cases, 296
66%
Inoperable cases both medical and surgical no hope of cure
196
189 cases with either no operation colostomy or laparotomy
7 cases with operation for palliative reasons with resection
34%
Operable cases for cure with resection
99
Operable case arrested 8 years with colostomy and radium
1

Chart 1. The operability for cure in this series of 296 cases is 34 per cent. In this group this figure is low as compared to 73.6 per cent as reported by Cattell and 53.2 per cent as reported by D. F. Jones, of Boston. Operability depends upon two main factors: (a) the class of patient admitted to the clinic. Group clinics depending upon referred patients for the greater number of their cases will have, on the whole, a better class of patient and an earlier diagnosed lesion than the general hospital in a large city receiving the charity patient from the ambulance in the street. (b) The skill of the operating surgeon. The more experienced the surgeon, the greater the number of cases he will operate upon.

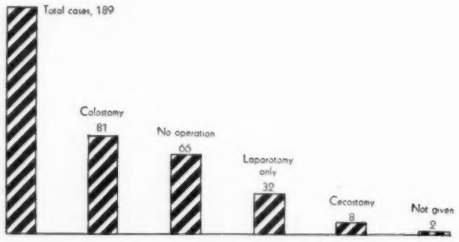


Chart 2. Inoperable cases total 189 from a total of 296. Seven cases with resection without hope for cure are excluded. Deaths following palliative procedures were as follows: 10 died following colostomy; 16 died in the hospital without operation; 5 died in the hospital following laparotomy but without colostomy; no deaths followed cecostomy.

PATHOLOGY

The one hundred cases reported in this series as operable for cure have had microscopic pathological diagnoses. The sections have not been graded according to Broder. Up to this time their relationship to the end-results is, therefore, not available. Biopsies were performed in every case of the inoperable group in which a tumor could be reached.

OPERATIVE PROCEDURE

Multiple versus single stage operations. The discussion which is ever present as to whether multiple stage or single stage operations give the best results has been of some interest to us in examining this series. Fundamental physiological and operative principles should be borne in mind in the choice of operations for these patients, and should include: (a) as short an operation as possible which is consistent with a complete removal of the growth and gland bearing area; (b) the principle of self-inoculation against peritonitis.

These two principles find their application in the advocacy of multiple stage procedures. Our own experience does not warrant any specific recommendation in this matter. We believe that any particular set of rules to be followed in every case is not to be accepted.

It has been our impression that the use of the multiple stage operation in the hands of younger surgeons, both as to years and experience, is a far safer maneuver in the majority of cases. To be dogmatic on this point, however, is to lose that fine sensitiveness to the patient's ability to withstand trauma which makes for a good surgeon and a cured and living postoperative patient.

Efforts should be made, in judging these patients as to type of operation, to save the sphincter in as many cases as possible. In 8 patients, 2 of whom died, resections were performed, saving the sphincter. Seven of these were true rectosigmoid lesions, and the great temptation is to remove the growth by the abdominoperineal route. Undoubtedly, a number of cases can be saved the inconvenience of a colostomy if experienced surgeons will attempt procedures such as these, but not sacrificing the principle of removing

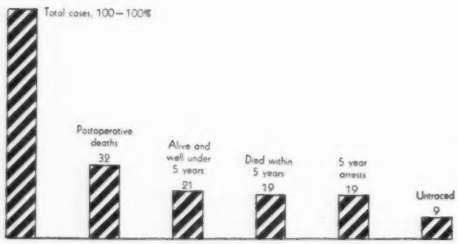


Chart 3. Included in the 32 postoperative deaths are 2 cases in which only the first stage of a multiple-stage procedure was carried out.

The 19 5 year arrests represent 34.5 per cent of 55 resections. Note that the figure at top of column indicates percentage as well as number of cases.

Fig. 1. Specimen removed 1 year after a proctoscopic examination by a competent observer, who found abnormality in neither the rectum nor sigmoid.

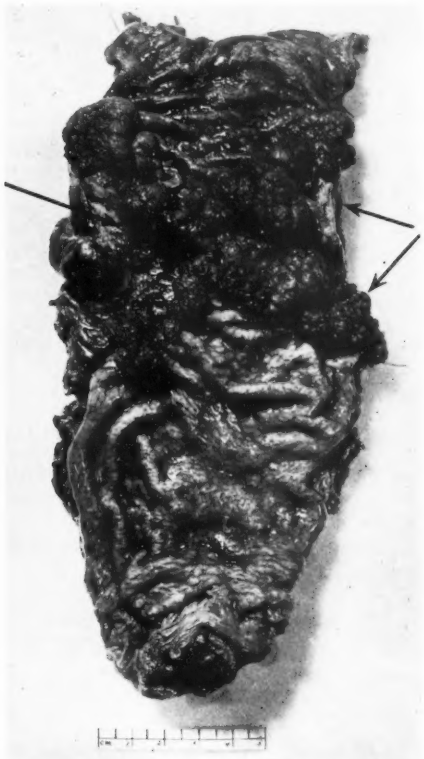


Fig. 2. Specimen removed following three biopsy examinations with report of non-malignant adenoma. Carcinomatous degeneration in one portion only. Arrow at left, carcinoma; at right, adenoma.

the gland-bearing area for saving the sphincter. It is hoped additional progress in technique will bring results along this line.

ANESTHESIA

In the last 2 years, the use of spinal anesthesia has been of considerable help to us. With the use of pantocaine up to 2.5 cubic centimeters, introduced between the first and second lumbar vertebræ, we have gotten between 2 and 3 hours of anesthesia, and when the operation has been completed in this time the patients have shown less shock. Cyclopropane and ether have come into favor when spinal anesthesia is not used. In the great majority of these cases reported the patients were operated upon with open ether anesthesia.

TRANSFUSIONS

We believe that the free use of transfusions before and after operations, regardless of the apparent condition of the patient, leads to fewer complications and a smoother convalescence. This applies to the first as well as the second stage of the multiple stage operation.

OTHER GENERAL CONSIDERATIONS

It has been our own experience in a comparatively small number of cases that the

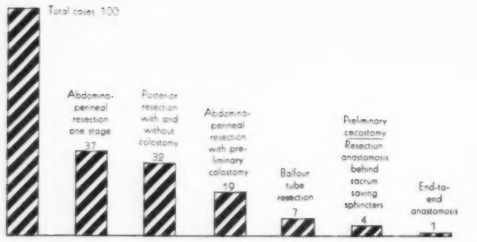


Chart 4. There were 11 Lahey procedures in the 19 abdominoperineal resections. There were 46 single stage, and 54 multiple stage, procedures performed in this group.

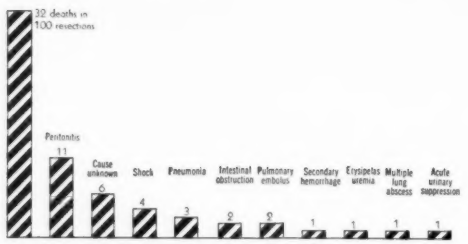


Chart 5. Peritonitis headed the list as usual. Two cases developed bilateral suppurative parotitis. Those cases in which autopsies were not performed and the cause of death was questionable, were listed as unknown causes. In this group are undoubtedly some due to peritonitis. Note that the figure at top of all but first column represents the number of deaths in a total of 32 and the percentage of deaths in 100 resections.

most satisfactorily functioning colostomies are those in which the gut has been pulled through the skin and anchored to it without suturing the peritoneum.

The Levine tube is of great value in any abdominal operation and should not be forgotten in these cases. The general tendency is to use it only if the patient vomits. We have all seen enormous dilatation of the stomach without vomiting. It should be introduced at least twice during the first 48 hours, if the patient's condition is in any way unsatisfactory, particularly when large quantities of saline are given intravenously. In these cases a fair amount of fluid finds its way into the intestinal tract. Our own experience has shown patients with full stomachs following infusions, and not having taken fluid by mouth.

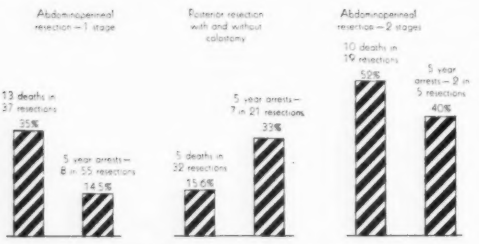


Chart 6. What type of operative procedure has given the best 5 year arrests, with the lowest mortality? *Posterior resection*, with or without colostomy. In comparing the figures making up this chart, several points must be made clear. The mortality figures are based upon the entire series. The 5 year arrests must necessarily be based upon those patients operated upon between 1924 and 1931. This gives a small figure in the two stage abdominoperineal because this procedure had not been popularized at that time. Posterior resection has given the best results in this series because it is a less formidable procedure and because the operative time element is shorter. Operating time plays a significant rôle in the mortality rate as shown in a later chart. The number of two-stage abdominoperineal resections performed has increased materially since 1931.

In listing these 5 year arrests, it might be pointed out that there were, in addition, 5 other patients operated upon prior to 1924 and representing 4 of our best 5 year or more arrests, namely 13, 14, 18, and 21 years.

We have used pre-operative intraperitoneal inoculation in 3 cases, with 3 fatalities, and rather naturally feel that self-inoculation, as given in the multiple stage procedure, may be safer in our hands.

Our own experience in this series of cases with radium therapy has been almost nil. The one outstanding case is that listed of an 8 year cure of an operable case with colostomy and radium treatment. Its use in operable cases has led, in other hands, to great comfort for some patients.

The statistics on Brindley of Temple, Texas, in the use of the hot knife with posterior resection following colostomy are extremely low as to mortality, but here again familiarity with procedure and sufficient material for such procedure plays a large part in such results. Our own experience with the lowest mortality in posterior resection is in accord with his figures.

Periodic adequate health examinations including the intelligent use of the proctoscope, will reveal a surprising number of rectal polyps. Their removal will go far toward not only the early diagnosis but the prevention of cancer of the rectum.

While these statistics as to the number of cases seen are considerably lower, and the

operative mortality higher than those found in the larger clinics, it is our impression that they will correspond rather closely to those of any general hospital organized as the staff of St. Luke's Hospital is organized.

We should like to point out that the majority of these patients are private patients or patients sent into the ward by the operating surgeons as special cases, and were under their personal management and care. Thirteen surgeons performed the one hundred operations listed in the operable for cure classification. There has been no definite policy throughout the hospital as to the management and care of these patients, each individual choosing his pre-operative and postoperative management according to his experience and judgment.

In a general hospital, it seems feasible to assign an operating team to this group work in the treatment of carcinoma of the rectum, the results to be reported after the lapse of a fixed period, such as 2 years. In order to increase the number of cases coming to the general service, a well organized proctoscopic clinic, being an integral part of a gastro-intestinal clinic, will be of value. Those men in the group who avail themselves of the benefits arising from this clinic will have a better knowledge of the physiology and pathology of the intestinal tract, which in turn will improve their pre-operative and postoperative management. This plays no small part in the cure of this disease. In those hospitals in which special cases are sent in by members of the staff to be operated upon by them, the advice and assistance of the then assigned operating team should be available.

This last suggestion we believe is justified and is urged upon general hospitals in order to bring the treatment and handling of these patients more nearly in line with the results of the group clinic.

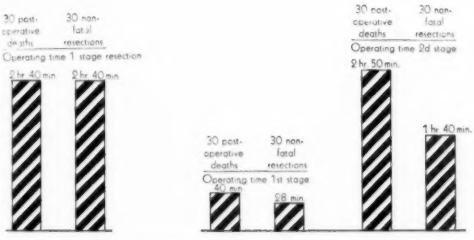


Chart 7. This chart is made to show the relation of the operating time in the single and multiple stage procedures, in 30 fatalities and 30 non-fatal cases of resection, with comparable number and kind of procedure in each. In the single stage, the time is the same. In the multiple stage, the second maneuver is 1 hour and 10 minutes less in the non-fatal cases. This has some bearing on the mortality rate. In those cases in which the operating time is prolonged and hemorrhage is uncontrolled, the additional length of time plays a most important part in increasing the mortality. Very careful hemostasis and a prolonged operating time are consistent with the lower mortality rate. Operating time can be reduced only when familiarity of procedure, which comes with frequent operating on this type of case, can be attained and maintained.

SUMMARY

1. Twelve years' experience in the treatment of carcinoma of rectum at St. Luke's Hospital, New York City, is reviewed.
2. One hundred operable for cure cases with resection are analyzed.
3. The operability was 34 per cent.
4. The operative mortality was 32 per cent.
5. The percentage of 5 year arrests (19 cases in 55 resections) was 36 per cent.
6. Posterior resection with or without colostomy gave a distinctly larger number of 5 year arrests with a lower mortality than other procedures.
7. Non-fatal resections showed a shorter second stage procedure by 1 hour and 10 minutes than similar groups of fatal resections.
8. Group study and group management of cases of carcinoma of rectum in general hospitals are urged.

REFERENCES

1. Brindley, M. D. Carcinoma of rectum. J. Am. M. Ass., 1937, 108: 37–43.
2. Cattell, R. B. Improvements in treatment of cancer of rectum. J. Am. M. Ass., 1936, 107: 2011–2016.
3. Jones, D. F. Carcinoma of colon and rectum. Bull. N. Y. Acad. Med., 1936, 12: 509–518.

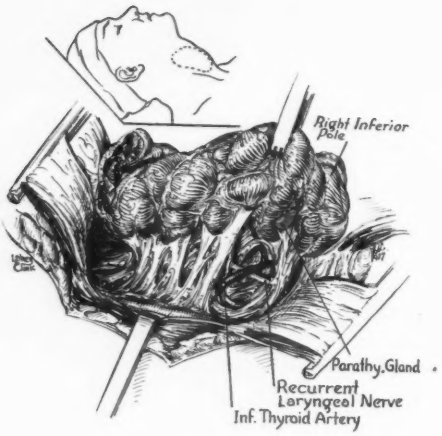


Fig. 2.

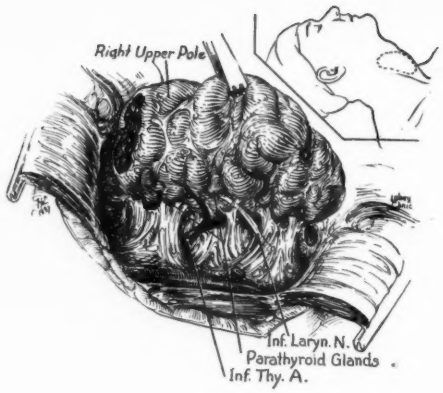


Fig. 3.

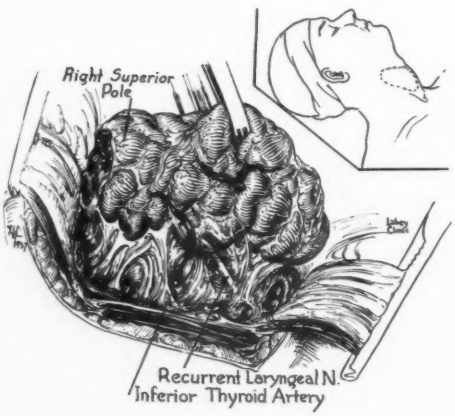


Fig. 4.

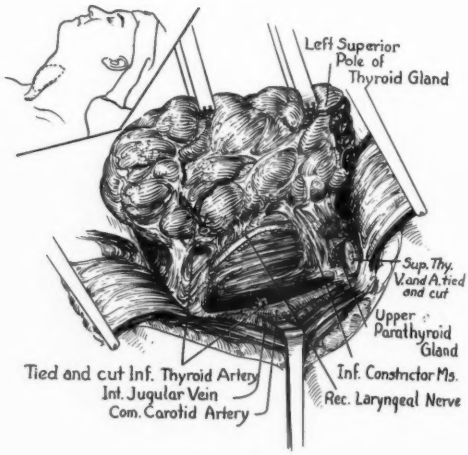

Left Superior Pole of Thyroid Gland
Sup. Thy. V. and A. tied and cut
Upper Parathyroid Gland
Tied and cut Inf. Thyroid Artery
Int. Jugular Vein
Com. Carotid Artery
Inf. Constrictor Ms.
Rec. Laryngeal Nerve

Fig. 5.

Fig. 2. Illustration made at the operating table with the thyroid gland elevated out of its bed and inverted. The inferior thyroid artery is demonstrated and the typical relationship of the recurrent laryngeal nerve to the inferior thyroid artery is shown. Note the relationship of the lower parathyroid gland.

Fig. 3. This illustration likewise was made at the operating table. Note that in this case the recurrent laryngeal nerve runs over the lower branch of the inferior thyroid artery, and is buried beneath a tongue of thyroid tissue near the upper pole, at which level it enters the larynx. Note the typical position of the lower parathyroid gland, between the branches of the inferior thyroid; note the upper parathyroid which, of all parathyroid glands, is the most constant in location, most easily found, in its position against the larynx. This thyroid gland has been elevated and inverted.

Fig. 4. In this operative dissection, the recurrent laryngeal nerve runs beneath both branches of the inferior thyroid artery in its typical relationship.

Fig. 5. In this operative dissection as in the others, the superior thyroid pole has been freed and cut, the gland has been elevated from its bed and inverted, and the inferior thyroid artery has been cut between ties to permit complete exposure of the recurrent laryngeal nerve up to the point at which it enters the larynx. This extent of exposure will rarely be necessary. Note again the quite constant location of the superior parathyroid gland.

Routine Dissection and Demonstration of Recurrent Laryngeal Nerve in the Subtotal Thyroidectomy—Frank H. Lahey

CLINICAL SURGERY

FROM THE DEPARTMENT OF SURGERY, THE LAHEY CLINIC

ROUTINE DISSECTION AND DEMONSTRATION RECURRENT LARYNGEAL NERVE IN SUBTOTAL THYROIDECTOMY

FRANK H. LAHEY, M.D., F.A.C.S., Boston, Massachusetts

UP to the present it has been the custom for surgeons operating upon the thyroid gland to take the position that they do not want to see the recurrent laryngeal nerve, that if the nerve is seen it is endangered, and that as the result of stretching and manipulation consequent to its exposure, recurrent laryngeal paralysis may result. It has been the custom of thyroid surgeons to avoid injury to the recurrent laryngeal nerve by leaving sections of thyroid tissue over the region where the nerve should be and by avoiding in the dissection the region in which the recurrent laryngeal nerve is presumably located. It has frequently been stated also that technical measures directed toward high elevation of the lateral lobes of the thyroid gland out of their beds could so stretch the recurrent laryngeal nerve that paralysis might well occur.

About 3 years ago we instituted the policy of dissecting the recurrent laryngeal nerve in practically every type of thyroid operation. In the year 1935, 998 thyroid operations were done; in the year 1936, 1,148; and during 1937 more than 1,300 thyroid operations have been done. It is obvious that in hundreds of cases the recurrent laryngeal nerve has been palpated while moderately on the stretch, dissected, and so visualized that in each case it could be clearly demonstrated to assistants and visitors. It has been demonstrated and visualized on one side, or on both sides, in patients with exophthalmic goiter, with a recurrent type of goiter, with toxic adenomas, with large and small discrete adenomas, with deep intrathoracic goiters, and in patients with all grades and types of malignancy. In none has there been either immediate or later paralysis or changes in position of, or motion in, the vocal cords as result of these dissections.

As the result of this large experience with the anatomical relationship between the recurrent laryngeal nerve, the inferior thyroid artery, the trachea and the thyroid itself, we are certain that there is a very definite constancy in the location of this nerve, and that this constancy of location occurs no matter what type of goiter is present, regardless of how large it is or how deep it is situated in the chest. Formerly it was considered that when the intrathoracic goiter had extended deep into the mediastinum there was danger that the downward extension of the intrathoracic masses of thyroid tissue would result in downward pressure and stretching of the recurrent laryngeal nerve. We have now removed several hundred intrathoracic goiters, many of which have extended down to within a rib or two of the level of the diaphragm (Fig. 1). Following these removals we have done dissections and demonstrations of the recurrent laryngeal nerve on the side on which

Fig. 1. The depth of this intrathoracic goiter is outlined by arrows and the degree of tracheal deviation by dashes. If an intrathoracic goiter ever distorts the course of the recurrent laryngeal nerve, in this type of goiter the nerve should be displaced. In a large number of cases similar to this the recurrent laryngeal nerve has been dissected and found to be in the normal position.

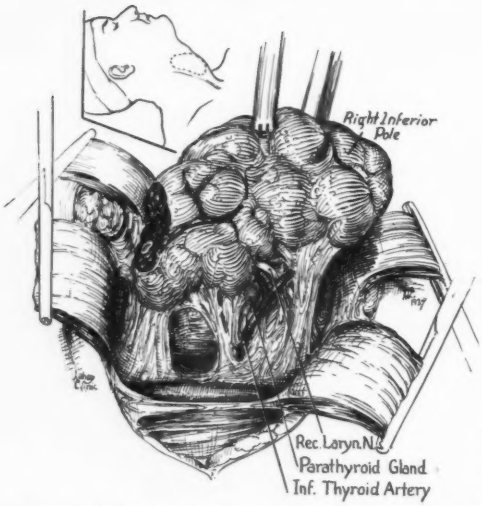


Fig. 6. With the gland mobilized and inverted, the typical and most common relationship is shown of the recurrent laryngeal nerve to the lower pole of the gland and the inferior thyroid artery. Note the direction of its course toward its point of entrance into the larynx; also the quite common location of the inferior parathyroid gland.

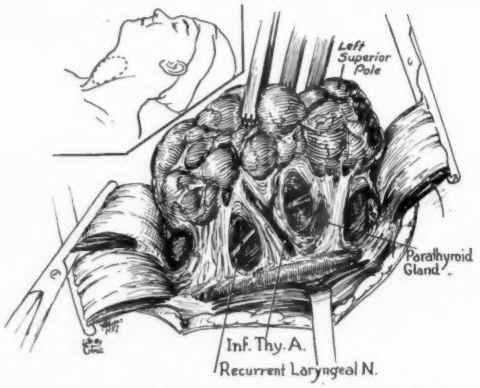


Fig. 7. In this operative dissection the nerve has been exposed up to the point at which it enters the larynx. Note its division into two branches, one larger than the other. Presumably this is an extralaryngeal separation of the nerve into the segments to supply the abductors. We have repeatedly seen this extralaryngeal division in the course of our operative dissections of this nerve. Note again the quite constant location of the parathyroid gland in its position against the larynx.

the intra-thoracic extension has been located. In all of the cases the recurrent laryngeal nerve has not been stretched, and has been in its usual position, except that frequently it is pushed more closely against the trachea than usual.

In the course of performing several thousand thyroidectomies, the thyroid lobes routinely have been grasped with our own special grasping forceps and not only have both lateral lobes been dislocated from their beds after detaching them laterally from the internal jugular vein, but they have been so dragged upon that they were displaced across the trachea so that the dislocated lobe rested bottom side up upon this structure. Temporary or permanent paralysis of the recurrent laryngeal nerve has not occurred following this procedure. During the last 3 years we have repeatedly located the recurrent laryngeal nerve in the cellular tissue below the main trunk of the inferior thyroid artery by palpating it somewhat on the stretch and have taught every surgical fellow in the clinic who has served as an assistant to locate the recurrent laryngeal nerve at this point by palpation. As the result of this procedure no recurrent laryngeal nerve paralysis has occurred.

The course of the recurrent laryngeal nerve is constant but the shape and extension inferiorly and laterally of the thyroid tissue of the lower pole of the thyroid gland are quite inconstant. Not infrequently there will be extensions of thyroid tissue from the posterior aspect of the lower thyroid pole. Often these extensions will so approach the course of the recurrent laryngeal nerve that this structure, unless visualized and protected, can easily be injured.

The plan of leaving a strip of thyroid tissue over the region where the recurrent laryngeal nerve is presumed to be, because of fear of injury to that nerve, not infrequently results in leaving too large segments of thyroid tissue; thus inadequate thyroid tissue is removed and the hyperthyroidism persists or recurs.

Every surgeon in the clinic operating upon thyroid glands has learned to dissect and demonstrate the recurrent laryngeal nerves. With the lateral lobe of the thyroid grasped in double hooks and pulled up out of its bed, the common carotid artery and internal jugular vein then are dissected and held outward by a special blunt retractor, thus exposing the areolar tissue between these vessels and the trachea. In this region the trunk of the inferior thyroid artery is demonstrated. As is shown in Figures 2 to 7, the angle of approach of the recurrent laryngeal nerve is quite constant as it passes either behind or in front of the inferior thyroid artery to reach the point at which the nerve enters the larynx by passing beneath the lowest fibers of the inferior constrictor muscle where this structure is attached to the horn of the

thyroid cartilage. At this point, just below the inferior thyroid artery, the recurrent laryngeal nerve can usually be palpated, and it is at this point that we routinely demonstrate the nerve trunk.

The trunk of the recurrent laryngeal nerve at this point is considerably larger than the lead in the average magazine pencil. It is of such definite thickness that it can be palpated easily as it is pushed and rolled against the cartilaginous rings of the trachea. The course of the recurrent laryngeal nerve beneath and above the inferior thyroid artery can usually be demonstrated by introducing a pair of right angle clamps over the nerve and beneath the artery, opening the clamps gently.

Although this method of demonstrating the trunk of the recurrent laryngeal nerve below the point where it passes behind the inferior thyroid artery, does not in many of the cases result in exposure of the nerve from the level of the inferior thyroid artery up to the point at which the nerve enters the larynx, its course here may very readily be visualized by placing a finger on the tip of the thyroid cartilage and laying a hemostat from that point down to the point where the trunk of the nerve is in plain view.

It is at this point, between the horn of the thyroid cartilage and the point where the nerve passes under or over the inferior thyroid artery, that the greatest number of injuries to the recurrent laryngeal nerve is produced. It is in this short course that the nerve is sometimes imbedded in thyroid tissue, or is frequently overlapped by thyroid tissue and pressed against the laryngotracheal junction. It is at this point that the upper branch of the inferior thyroid artery, as it rests against the trachea and enters the gland, is not infrequently torn in performing subtotal thyroidectomy. Attempts to control bleeding, at this laryngotracheal junction, from the upper branch of the inferior thyroid artery after the surface of the gland has been cut across anteriorly, sometimes result in passing the hemostat so deeply between the trachea and the stump of remaining thyroid tissue that the nerve is unknowingly caught at its most anterior point, just before it disappears behind the inferior constrictor muscle.

If the trunk of the recurrent laryngeal nerve has been demonstrated and its course visualized, it is obvious that attempts to control bleeding at this point from the upper branch of the inferior thyroid artery will endanger the nerve; a local ligature should not be applied, but the main inferior thyroid artery outside the point where the recurrent nerve passes over or beneath it should be ligated. By following this procedure, injury to many a recurrent laryngeal nerve will be avoided.

When the recurrent laryngeal nerve passes in front of the inferior thyroid artery, as it occasionally does, the course of the nerve up to the point at which it enters the larynx is usually much clearer than when it passes beneath the artery, and not infrequently in such cases the entire trunk of the nerve up to its point of disappearance into the larynx can be seen. At times the sharp angulation of the nerve as it passes into the larynx can be demonstrated. In an occasional case the nerve, as shown in Figure 7, may split into the relatively large group of fibers innervating the adductor muscles of the cords, the cricoarytænoideus lateralis, and the relatively small group of fibers innervating the abductors of the cords, the cricoarytænoideus posterior.

In the course of performing subtotal thyroidectomy and the dissection and demonstration of the recurrent laryngeal nerves, parathyroid bodies are frequently encountered and are always looked for. No attempt is made, however, to dissect these structures since the situation here is quite different from that of demonstration of the recurrent laryngeal nerve in that the parathyroids are dependent upon small end vessels for their blood supply and attempts to dissect and demonstrate these structures could well interfere with their blood supply and result in loss of their function.

CONCLUSIONS

A technical method of dissecting and demonstrating recurrent laryngeal nerves has been employed for over 3 years in performing subtotal thyroidectomy in more than 3000 cases. We have refrained from publishing this plan or advocating its use until it had been employed for a sufficient time and in a sufficient number of cases so that we could safely speak about it after a justifiable amount of experience.

We have all illogically accepted unproved statements of the past that manipulations around the region of the recurrent laryngeal nerve would produce interference with the function of that nerve.

This method, in competent hands (and no plan should be expected to fit incompetent ones), will not increase but rather definitely decrease the number of injuries to the recurrent laryngeal nerves. It will also encourage the removal of larger amounts of thyroid tissue, without added danger to the nerves.

BILATERAL NON-TUBERCULOUS ILIOPSOAS ABSCESS

MARIE ORTMAYER, M.D. Chicago, Illinois

CHRONIC psoas abscess of other than tubercle bacillus origin is rare. No instance of *bilateral* non-tuberculous iliopsoas abscess was found in the literature. The one to be reported occurred following pneumonia in a young girl who was ill with fever for 5 months and recovered after drainage of the abscesses.

Tuberculous psoas abscess is a well known condition, of considerable frequency especially in children, originating from tuberculous caries of the lower dorsal or upper lumbar vertebræ, as a rule, and traversing downward along the planes of psoas muscles to point above, but most commonly below, Poupart's ligament.

Acute iliopsoas abscess due to the Staphylococcus aureus or albus, or streptococcus, results, according to textbooks on surgery (2), from trauma or strain of the muscle fibers with resulting hematoma and infection with pus formation. L. Long cites 6 cases of such abscess, 4 in boys under 17 years of age with a history of injury preceding the onset, 1 in a woman during the puerperium, and the sixth in a boy of 17 years ill for a year after. The first 5 had quick and permanent recovery following drainage of the abscesses from "behind the iliac fascia or behind the iliopsoas muscles." In a discussion, Dr. Urban Maes cited 5 acute cases he had seen, without a previous history of injury but following furuncle or carbuncle, Staphylococcus albus being the infecting agent. Reporting of so many instances by two men raises the question of the possible high frequency of "acute iliopsoas abscess" in spite of the meager number reported in the literature.

Curiously enough, chronic iliopsoas abscess of other than tubercle bacillus infection has its origin, as in the author's patient, not from caries of the vertebræ, but from perforated empyema, and is found, therefore, under the subject of complications of empyema, as empyema necessitatis or migrans. The literature before 1900 contains most of the references, because spontaneous perforation of empyema is much less common since x-ray has been added to the diagnostic armamentarium of chest diseases. Unusual positions of encapsulated empyemas, such as the basal and mediastinal collections of pus, are now more readily detected, while a prolonged course of empyema without surgical drainage is the exception nowadays. Spontaneous perforations of empyema, however, still occur (6, 10, 16, 27). Rupture into the esophagus, the pericardium, into the stomach or abdominal cavity via the diaphragm, into the urinary passages, into the bowel and through the visceral pleura into the lung are cited. "Pulsating pleurisy," a dramatic variation of the escape of pleural pus through the chest wall, usually in its thinnest places near the sternum or lateral to the pectoralis, is mentioned in all the textbooks. Rarely mentioned, but "very remarkable are those which pass down the spine and along the psoas into the iliac fossa, and simulate a psoas or lumbar abscess" (21). Abscesses of this latter type are discussed in this paper.

Because of the difficulties in diagnosis and the extreme rarity of instances reported, in the English language especially, the following patient's course is given in some detail.

C. D., a girl aged 15 years, entered the hospital November 18, 1936. She had been well and in school until she "caught cold" 5 days previously. After remaining up and about for 2 days she developed "severe general abdominal pain," followed by a chill lasting 30 minutes, a temperature of 101 degrees and inability to void. Her physician sent her to the hospital with a diagnosis of "acute abdomen."

On entrance, the temperature was 101 degrees, the pulse 130, and the respirations 40. Well developed and fairly well nourished, this girl seemed acutely ill. Her expression was apprehensive, alæ nasæ moving marked, the pharynx moderately injected, the cheeks flushed, and respirations shallow and rapid. Postnasally, there was a thick greenish discharge. The right lung was hyperresonant in its upper and middle lobes and dull over the lower. Fine râles were heard in the middle lobe, diminished breath sounds over the lower lobe without râles. By the following morning, the left lung had developed flatness in the base with tubular breathing, but no râles. The heart was rapid and regular, not enlarged. A murmur, almost presystolic in time, was present, loudest over the pulmonic area. The abdomen was rigid, almost boardlike, and extremely tender, most marked in the upper right quadrant. Marked tympanites was noted but no masses were palpable. The rectal and vaginal examinations were negative. The extremities were normal with normal reflexes.

Blood count showed hemoglobin 80 per cent; red blood cells 5,130,000; white blood cells 62,000; differential blood count: polymorphonuclears, 98 per cent, lymphocytes, 2 per cent. The urine was normal except for a trace of albumin and occasional pus cell. The sputum was scant, mucopurulent, and contained many diplococci resembling pneumococci. At this time no x-ray pictures were taken. Diagnosis: bilateral lower lobe pneumonia.

The patient appeared extremely toxic; cough was frequent though unproductive of much sputum; respiratory embarrassment and pains "in both lungs" were present for

From the Department of Medicine, University of Chicago and Women's and Children's Hospital.

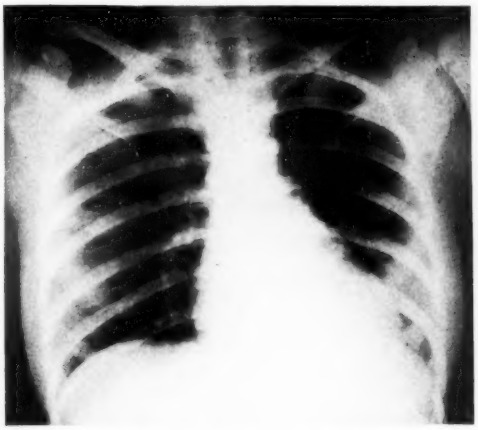


Fig. 1. Anteroposterior view November 28, 1936, showing relatively clear right chest, shadows in lower left chest with obliteration of diaphragm and stomach air bubble, but with the heart shadow hiding the probable pathological condition in the left posterior pleural cavity.

Fig. 2. Left anterior oblique roentgenogram which was taken on December 8, 1936, showing shadow in the left posterior costomediastinal pleural cavity. From this infected area somewhere pus can have perforated downward.

3 days, for which small amounts of codeine and morphine were given. Abdominal pain, generalized or shifting, continued for 10 days; catheterization was necessary for 2 days; diarrhea was quite persistent. Both lower lobes of the lung became dull to flat, with absent fremitus, with minimal râles, with distant tubular breathing only near the spine. Tympanites and "high standing diaphragm" interfered with evaluation of signs. The right chest gradually cleared and breath sounds came through by the end of 2 weeks. Though distention of the abdomen decreased at this time, tenderness was marked over the spleen and in both inguinal regions. The temperature had fluctuated daily from 100 to 104. The white blood count dropped in the first 4 days from 62,300 to 32,600 with the polymorphonuclears 97 per cent.

The x-ray diagnosis of this period was: Probably unresolved pneumonia of the left base. Fluoroscopic check for fluid was inconclusive, as the patient could be moved with difficulty (Fig. 1).

Toward the end of the third week of her illness, the patient had a chill lasting 3 minutes. A consultant, finding a diagonal line of flatness posteriorly left, extending from the sixth vertebral spine downward almost to the posterior axillary line with egophony, bronchial breathing, and crepitant râles above it, made a diagnosis of left lower lobe atelectasis following bilateral lower lobe pneumonia. A second fluoroscopic examination verified the triangular shadow in the left chest near the spine and back of the heart (Fig. 2). Left posterior pleural sinus pleuritis with effusion or suppuration was also considered, but as thoracentesis on three occasions by the internes failed to yield fluid or pus, the diagnosis was in doubt. The diagonal left posterior pleural flatness and its accompanying x-ray shadow gradually receded in the next few weeks and had completely disappeared by the end of the second month of illness.

Search continued for the cause of the temperature, which after the first month had dropped from 102 degrees to normal and remained so for 36 hours, only to rise again and remit once daily, in quite irregular fashion, from 99 degrees or thereabouts to over 100, 101, at times even to 103 degrees, for 2½ months more. The red blood count had dropped to 2,900,000, the hemoglobin to 52 per cent, and the white cells to 13,800 with 58 per cent polymorphonuclears. The early diarrheal stools were repeatedly negative for occult blood, ameba, ova, pus and bacilli of the typhoid group. No tubercle bacilli were found in the sputum, only pus cells and lance-shaped diplococci. On the blood: cultures yielded no growth; the Widal, typhoid, paratyphoid, and undulant tests were negative; the tuberculosis fixation was slightly positive. The area of infiltration of the Mantoux skin test was 1 centimeter at the end of 48 hours. In the urine mild traces of albumin were found, 15 to 20 pus cells and colon bacilli. Pyelograms, colon roentgenogram, and spinal x-ray films were normal.

Late in the second month of illness, the patient began to complain of occasional vague abdominal cramping, indefinitely located, but later referred to both lower quadrants where some rigidity and tenderness were noted, especially left.

After a week, the rigidity of the abdomen became less marked and pain was practically absent. Firm masses could now be felt fixed in both iliac fossæ. The left was the better outlined and the larger and lay just below the anterior superior spine of the ilium. For a month these masses definitely increased in size, though they were not tender. They were shown to be separate from the pelvic organs and colon. Free motion of the hip joints was possible, without pain!

Three and a half months after onset of illness in this girl, the final medical opinion was:

In view of the stormy onset with "cold" and anuria, which was the beginning of a bilateral pneumonia, or possibly even of bilateral pleurisy with effusion; in view of the leucocyte count of 63,000 with persistence of polynuclear neutrophils in high percentage; the finding of the triangular area of flatness occupying the posterior left pleural sinus position, with its gradual recession and clearing; the persistence of temperature in spite of this clearing; the indefinite abdominal pain appearing at the end of 2 months' illness, with localization of rigidity and tenderness in both lower quadrants and the detection of bilateral masses, gradually enlarging and fixed over the iliopsoas

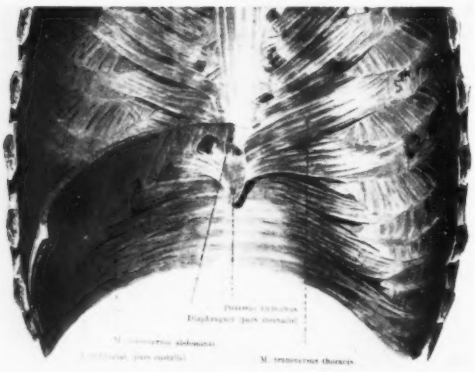


Fig. 3. Anterior attachments of diaphragm (viewed from below and inside.) Illustrates (as at *1, 2, 3*) points through which pus from anterior pleural sulcus could perforate downward. (From Spalteholz.)

muscles, I am forced, in spite of the failure to obtain pus on puncture from the pleura, to make a diagnosis of *low grade pus infection, originating probably from a left posterior encapsulated and perforated pleural sinus empyema and traveling via the posterior mediastinum and retroperitoneum downward in front of both psoas sheaths, to localize as bilateral abscesses in the iliac fossæ.*

These two abscesses were drained extraperitoneally above Poupart's ligaments near the anterior superior spines of the ilium, in front of the psoas sheaths, beneath the abdominal musculature and fascia. Direct smears from the pus on both sides yielded a gram positive diplococcus with capsule and a gram negative bacillus. Cultures failed on the diplococcus, but the gram negative bacillus grew anaerobically.[1] The guinea pig inoculated with pus from the left abscess failed to develop tubercle bacillus infection in 8 weeks. Necrotic material obtained from the right abscess was composed of fibrin, red cells, polymorphonuclear neutrophils, mononuclears, and plasma cells and upon microscopic examination was found to be granulation tissue.

With evacuation of pus, the temperature dropped promptly, the blood count became normal and both incisions healed. Very small, hard masses connected with the lower end of both scars could still be felt, but the patient felt well, had remained temperature free, and had gained weight on June 15, 1937, when last seen, 7 months after the onset of her illness.

Although there are some omissions in the recording of sequence of symptoms and chest findings in this patient and a failure to obtain pus from the left chest, possibly due to aspiration too far lateralward or to inspissation of pus, which cast doubt on the origin of these bilateral psoas abscesses from perforated empyema, there seems to be enough similarity to other reported cases, which were subjected to autopsy or clinically better established than the author's, to justify the diagnosis. A hematogenous or lymphatic origin bilaterally into the prepsoas fascia seems even more fanciful and would be more rare. The recovery of the pneumococcus-like organism (necrophorus is apparently a secondary invader in many pus processes) from both abscesses and the sputum, the occurrence of encapsulated empyema of the posterior pleural sinus in pneumonias, giving a roentgen picture similar to the author's (3, 14, 26), the tendency of left encapsulated empyemas to perforate and travel downward into the lumbar and iliac fossæ regions give credence to the conclusions.

Twenty-five previously published cases, all unilateral, 14 of them fully discussed by Bouveret (4, 5), have been found of "migrating abscess" originating from empyema (11, 13, 17, 19, 20, 23, 24, 28). One of these pointed somewhere in the anterior abdominal muscle region, 7 in the iliac fossæ or below Poupart's ligament, 1 as low as the knee, and 17 in the lumbar region between the lower rib margins and the iliac crests. *All these abscesses developed on the same side as the empyema* and in 19 in which the position of the empyema is definitely mentioned 5 only are right, 13 are left, and 1 is left and right. The latter, however, on autopsy showed the fistulous tract to be connected with the left empyema and an egg-sized encapsulated collection of pus on the right diaphragmatic pleura to be totally unconnected with the pus in the upper two-thirds of the left psoas. This instance of a 10 year old male published by Foot (11) is further interesting because of the very short illness of 3 weeks' duration and the dispersal of pus beyond the left psoas into the spinal canal as well as into the right back muscles. Of the 17 patients in which sex is mentioned, 10 are male. Eighteen whose ages are given range from 9 to 35 years, 7 of them in the second decade of life. The existence of empyema was known or suspected anywhere from 2 to 3 weeks to 1½ years before the diagnosis of distant abscess was made. Either the abscesses pointed spontaneously or they were drained surgically after a tumor presented in one or more of the three areas. When the perforation of the pleura by pus occurred early in the disease, and acutely, severe pain in the thorax was apt to be present, but not invariably so. In only 2 patients, Bouveret's own and that of the author, did the empyema disappear completely a considerable time before the discovery of the iliopsoas abscess. Bouveret's patient, a female of 31, had a proved left empyema which had been tapped 21 days after onset of left pneumonia with evacuation of 2100 cubic centimeters of pus. Repeated tapping and finally drainage, though it definitely improved

[1]Identified as Bacillus necrophorus by Dr. George Dack of the University of Chicago.

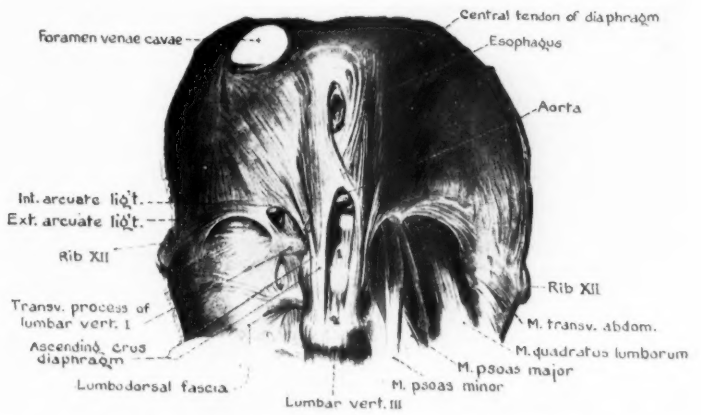


Fig. 4. Posterior attachments of diaphragm (viewed from below and inside). Illustrates hiatuses of aorta and esophagus, origins of left psoas muscles and sheaths from internal arcuate ligament, and quadratus and its sheaths from external arcuate ligament. (From Spalteholtz).

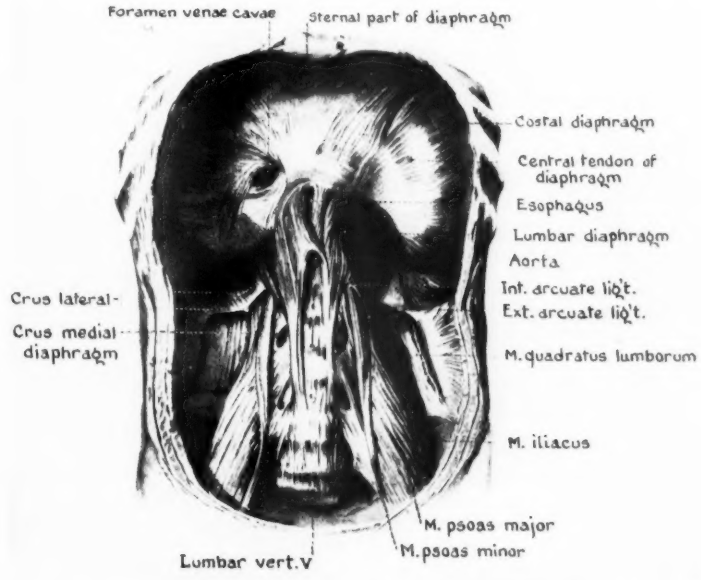


Fig. 5. Similar to Figure 4, but including lower projections of psoas and quadratus muscles on both sides. Illustrates how central descent of pus through the aortic hiatus could more easily spread bilaterally at third lumbar anterior to right and left psoas muscles, than if pus from the left pleura had pierced as far lateralward as the internal arcuate ligament.

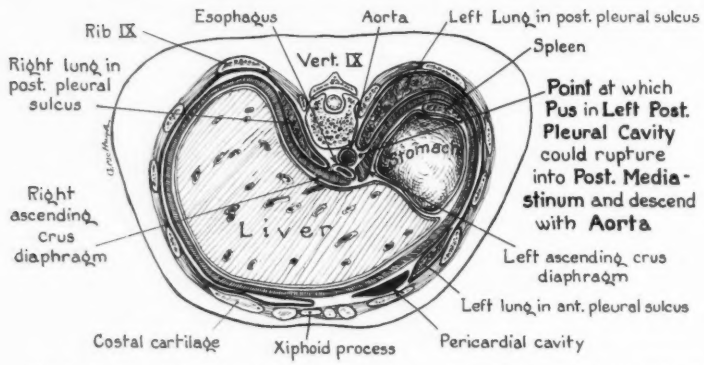


Fig. 6. Cross section at level of ninth thoracic vertebra. Illustrates relationship of posterior pleural space (outlined in deep black) to posterior mediastinum, aorta, and diaphragm. (Modified from *Topography of the Thorax and Abdomen*, by Peter Potter.)

the chest, did not reduce the temperature. Eventually, 13 months after her pneumonia onset, the patient evacuated pus spontaneously from the left groin below Poupart's ligament, with cure! Several patients had final clearing of the chest when the abscesses drained. Three of the abscesses developing in the left lumbar region were pulsating!—one of Courbon, in a female of 24 who recovered, a second of Owen-Rees, in a male of 9 years who came to autopsy (perhaps tuberculous pleurisy but with sinus tract from left pleura not from caries of vertebra), and a third of Dunin, also subjected to autopsy. Bouveret gives a very able discussion of the mechanics of pulsating pleurisy (5, 7) and the differentiation between these pulsating "migrating" abscesses and aneurism of the abdominal aorta.

When it is realized that of 19 patients in whom the outcome is definitely reported, 13 resulted in cure and 6 in autopsy it is not surprising that it is still a matter of conjecture as to the exact manner in which the perforation of these pleurisies results in migrating abscess.

The appearance of pus anteriorly among the muscles of the abdomen and pointing somewhere below the diaphragm seems to be due to rupture through the anterior pleural sulcus (20). Whether the pus travels *via* the anterior mediastinum just back of the sternum, through the known weak spot of the diaphragm between its sternal and costal origins, or through the interdigitations of costal diaphragm and anterior abdominal muscles, cannot be determined from reports (Fig. 3). The autopsy on Loomis' patient revealed the perforation in the "extreme anterior border" of the diaphragm, the fistula passing into the anterior peritoneum, leading over the liver and downward in front of the ascending colon to point above Poupart's ligament.

As to the psoas abscesses, J. J. Clark has contributed the most convincing proof *in vivo*.

He reports a male negro 35 years of age with a brawny swelling over the right thigh seen first complaining of pain over the right hip, developing 1 year after an attack of pneumonia. The swelling was treated as a localized abscess and drained. Later x-ray studies revealed a shadow in the right chest which was proved by thoracotomy to be empyema. Clark's serial x-ray studies after lipiodol injection into the right pleural cavity show two pools of dye above and behind the right diaphragm at the eleventh interspace; later, dye has passed "through the diaphragm close to the spine and under the right internal arcuate ligament"; then "a large cavity in the body of the psoas," which he believes proved by the striated appearance of the lipiodol "among the muscle fibers"; later: "a clot of oil over the right sacrum."

Whether one is entirely convinced or not of the interpretation of the reason for the striated appearance of the lipiodol in Clark's films, one must recognize this sole instance of x-ray visualization of the path taken by this pus as a valuable contribution.

It is assumed by most of the writers reporting instances of unilateral psoas or lumbar abscess that the pus has escaped from the empyema after perforating the pleura, through the internal or external arcuate ligaments (Fig. 4). Anatomically, however, it is difficult to visualize a bilateral spread, such as resulted in the author's patient, from perforation through either. Any perforation through the internal arcuate would seem to confine pus to a spread downward in front of, or within, the psoas on the same side, and through the external ligament to an equilateral path posterior to the psoas or within the quadratus lumborum (Fig. 5). The most careful autopsy

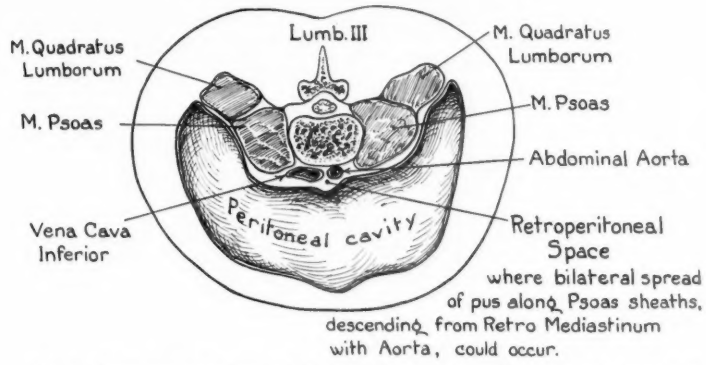


Fig. 7. Cross section at level of third lumbar vertebra. Illustrates relationship of retroperitoneal space to great vessels and right and left psoas muscles and point at which pus could spread bilaterally anterior to these muscles. (Modified from *Topography of the Thorax and Abdomen* by Peter Potter.)

examination, that in a patient of Foot (11), corroborates this hypothesis, for the sinus was found to pass from the left pleural space behind the left crus of the diaphragm, posterior to the internal arched ligament, into an abscess in the upper two-thirds of the left psoas. The psoas sheath was intact; the pus was deep in the substance of the vertebral border of the muscle (Fig. 5). Tees believes that he traced a lumbar abscess "invading the quadratus lumborum" through the external arcuate ligament when he surgically explored his patient. Certainly the location of pus in the pleura and the primary site where lysis has produced perforation, as well as the routes of dispersion available at this point, must all influence the eventual paths of the pus, even though conceivably pus may spread anywhere. The variety of ways in which tuberculous pus traverses downward (1, 15) illustrates the rôle that is played by the exact position of exodus of pus from spinal caries. The pus may hollow out the sheath of the entire psoas, bulging it to the size of a man's arm, or less commonly may stay completely anterior or posterior to its fascial sheaths. Prevertebral cold abscess is usually to left or right of center, uncommonly directly median and this may explain the infrequency of bilateral tuberculous psoas abscess. The bilateral abscesses of the author's patient were located anterior to the sheath of the iliopsoas muscles. If these both originated from the left posterior pleural sinus empyema, it is easier to assume central evacuation of pus from the mediastinum into the retroperitoneum with bilateral spread than rupture through the left internal or external arcuate ligaments (Figs. 6 and 7). That perforation from the left posterior pleural cavity into the posterior mediastinum occurs is proved by autopsy in the cases in which mediastinal abscess is found together with perforated empyema. Foot's (12) patient in whom the mediastinal pus lay anterior to the aorta and perforated the esophagus, as well as several of Knauer's perforating the esophagus prove this. It is not too great a flight of the imagination, especially when considered in the light of cross-sectional anatomy (25), to assume that pus so escaping could migrate downward along the great vessels between the crura of the diaphragm or through the esophageal hiatus.

As most of these reports were published in the early medical literature, it is not strange that bacteriology of the abscesses is so seldom mentioned. Usually the authors have merely stated that they were non-tuberculous. The direct smears herein reported demonstrating a diplococcus similar to that found in the sputum, resembling pneumococcus morphologically, and the additional gram negative bacillus found in the pus from the abscesses, with failure to develop tuberculosis in the guinea pig and apparent cure in the patient, establish the author's case, incomplete as it is, as bacteriologically the most fully studied in the literature. Knowledge of this report should stimulate more accurate study of the non-tuberculous psoas and lumbar abscesses occurring in the future.

SUMMARY

A case of bilateral iliopsoas abscesses originating from probable left posterior pleural sinus suppuration following pneumonia has been reported.

No other instance of bilateral abscesses of this type has been found in the literature.

The 25 other unilateral chronic abscesses, re-

ported in the literature as originating from perforated empyema and pointing at considerable distance below the diaphragm, are briefly reviewed and discussed.

The differences between these abscesses and the acute traumatic abscesses, usually of staphylococcus etiology, and tuberculous lumbar and psoas abscesses are mentioned, with special reference to anatomical variations in the paths of the migrating pus.

BIBLIOGRAPHY

1. Aschoff, Ludwig. Path. Anat., Jena: Fisher, vol. 2: 209.
2. Ashhurst, A.P.C. Surgery, Its Principles and Practice. 3d ed. Philadelphia and New York: Lea & Febiger.
3. Assmann, Herbert. Klinische Roentgendiagnostik, p. 329. Leipzig: Vogel, 1924.
4. Bouveret, L. Migrations insolites de l'empyème. Lyon méd., 1882, 40: 325–334, 365–374, 407–413, 437–447.
5. Idem. Traité de l'empyème, pp. 664–690. Paris: Baillière et Fils, 1888.
6. Clark, J. J. Empyema necessitatis with an unusual sinus tract. Internat. Clin., 1931, 1: 118–122.
7. Comby, J. L'empyème pulsatile. Bibliot. méd. Paris: Rueff et Cie, 1895.
8. Courbon. Gaz. d. hôp., 1870 (May 24), p. 237.
9. Dunin. Gaz. méd. de Varsovie, 1878, No. 23.
10. Dyson, J. E. Empyema with perforation of diaphragm and stomach. J. Iowa M. Soc., 1931, 21: 300.
11. Foot, A. W. Dublin J. M. Sc., 1873, 55: 40–42, 42–47.
12. Ibid., 1881 (July).
13. Froidure, L. Gaz. méd. de Picardie, 1889, 7: 228–231.
14. Herrnheiser, G. Kostomediastinale Schwarten. Fortsch. a. d. Geb. d. Roentgenstrahlen, 1923–1924, 31: 165–192.
15. Kaufmann, Edouard. Spez. path. Anat., 1922, 1: 879.
16. Knauer, H. Unusual complications of empyema. Arch f. Kinderh., 1935, 106: 156–159.
17. Lange, F. Ann. Anat. & Surg., 1883, 7: 107–110.
18. Long, L. Acute ilio-psoas abscess. South M. J., 1925, 18: 198–202.
19. Loomis, H. P. Proc. N. York Path. Soc., 1891, p. 58.
20. Morgan, J. H. Lancet, 1890, 2: 125.
21. Osler, William. Principles and Practice of Medicine, p. 671, 10th ed. New York and London: D. Appleton & Co., 1926.
22. Owen-Rees. Brit. M. J., 1858, Aug.
23. Paget, Stephen. Surgery of Chest, 1897, p. 227.
24. Picquet, M. Soc. de chir. de Paris, 1913, 39: 1341–1347.
25. Potter, Peter. Topography of the Thorax and Abdomen. University of Missouri, 1905.
26. Stoloff, E. G. Chest in children. Ann. Roentgenol., vol. 12: 269.
27. Tees, F. J. Empyema necessitatis and some allied conditions. Arch. Surg., 1923, 7: 321–331.
28. Berl. Klin. Wchnschr., 1889, 26: 649–653.

TENOSYNOVITIS OF THE LONG HEAD OF THE BICEPS HUMERI

V. L. SCHRAGER, M.D., F.A.C.S., Chicago, Illinois

TENOSYNOVITIS of the long head of the biceps is a non-specific inflammation of the tendon and its sheath. It is a shoulder complex characterized by pain, of various degrees, along the bicipital groove of the humerus, inability to raise the arm above the level of the shoulder, and diminution or loss of all other functions which put stress upon the tendon. It has a tendency to chronicity and, if untreated, may ultimately lead to muscular atrophy of the shoulder group of muscles and to a certain degree of loss of function.

The general literature, as far as I was able to ascertain, is silent on the subject, with the exception of some limited accounts in the French literature. Leclercq and Rouresco speak of tenosynovitis of the long head of the biceps humeri in connection with injuries of the shoulder in industries and the degree of disability thereof. They, evidently, took it for granted that the condition was well known and did not enter into further details. F. Pasteur,[1] medical colonel of the military hospital, Val-de-Grâce, recognized the condition in all its aspects, described it fully and clearly and raised it, unmistakably, to the rank of a distinct clinical entity.

Although I have been familiar with this condition for many years, interested my colleagues in the subject and presented clinical cases in clinics, my failure to record the facts in print gives Pasteur the priority of record.

Tenosynovitis of the long head of the biceps humeri is the most common cause of periarthralgias of the shoulder, a view which is fully shared by Pasteur.

In spite of the fact that the clinical picture is definite, constant, and easy of recognition, roentgenologists, orthopedists, and physiotherapeutists are mute on the subject.

ANATOMY

The biceps muscle has two heads: The short head arises from the coracoid process, close to the coracobrachialis. The long head arises from the top of the glenoid cavity. It takes insertion into the supraglenoid tuberosity and the glenoid ligament by a long tendon (9 cm.), which is either bifurcated or trifurcated at its origin. In the latter case, there is one intermediate portion attached to the scapula, and two smaller, collateral portions which diverge from each other and blend into the labrum glenoidale. The tendon glides over the head of the humerus, within the joint, invested by a synovial sheath (which is an evagination of the capsule), and then slides into the intertubercular, or bicipital groove, which is covered by an expansion from the pectoralis major and ends blindly opposite the insertion of the latter muscle.

PHYSIOLOGY, FUNCTION OF TENDON

The tendon of the long head of the biceps takes part in all the movements involved in either fixation or mobility of the upper extremity, which explains its vulnerability. It is an important factor in the dynamics of the upper limb. Together with the long head of the triceps, it helps to stabilize the humerus against the glenoid fossa (Steindler). According to Callander, the tendon of the long head of the biceps acts as a "standardizing brace" and "prevents any sudden impact between the head of the humerus and the underlying arch." Ducheme of Boulogne, in his work on the physiology of movements, assigns important function to the short head of the biceps and looks upon the long head as a mere supinator, flexor muscle.

The function of the tendon of the long head of the biceps can be summarized as follows:

1. It helps to maintain and coaptate the head of the humerus against the glenoid cavity.
2. It reinforces the capsular ligaments.
3. It prevents the head of the bone from being pulled too close upward under the acromium (Treves).
4. It supplements the deficiency of the subspinous muscle.
5. Both biceps heads are flexors and medial rotators of the arm at the shoulder; both are abductors, the long head abducts the arm and rotates it inward.

From the Department of Surgery Northwestern University Medical School.

[1]Some articles refer to E. Pasteur, others to F. Pasteur. I believe, however, that both are the same writer.

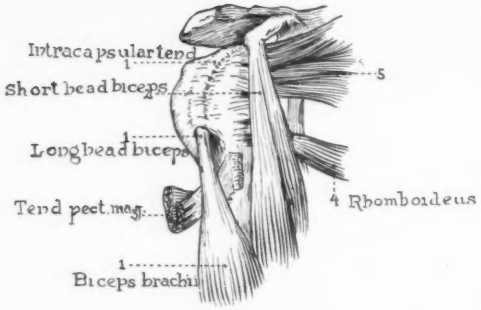


Fig. 1. Shows long head of the biceps entering capsule of shoulder joint. (From Testut's *Traité d'anatomie humaine.*)

ETIOLOGY

The etiological factors, although varied, are the following:

1. Trauma.
2. Metastatic infection from a systemic source.
3. Exposure to sudden changes of temperature, especially to cold and dampness.
4. Generalized effusions in serous cavities and spaces.
5. Rheumatic tendencies.

Trauma. Sudden muscular efforts in the course of infectious diseases are apt to initiate this syndrome, especially in the course of typhoid or influenza. Two of Pasteur's cases were the result of colon bacillus infection, while another occurred during an infection of bacillary dysentery.

Hard upward pull upon a cork screw of a tightly corked bottle may bring about the condition.

Fall upon the extended hand may produce the lesion. In this connection, it may be well to mention the occasional, coexisting pain in the corresponding shoulder in Colles' fracture, which is usually noticed some days after the fracture. This is, very likely, due to a coincidental injury of the tendon of the long head of the biceps which is overshadowed by the Colles' fracture. Fall upon the extended hand was the etiological factor in 23 of the 32 cases of Pasteur. In 8 of 20 cases, the patients were males past forty years of age.

Fall upon the shoulder is a frequent cause.

An attempt to prevent a fall may cause a sudden pain along the bicipital groove, which may be responsible for the syndrome.

Sudden jar of the shoulder among straphangers is apt to cause this condition.

Faulty position of the arm is another cause. False movements while the arm is in abduction and external rotation are also factors. Rheumatic patients may develop this syndrome on the slightest exertion, or false movement.

Muscle strain in systemic diseases may cause inflammatory changes in the tendon or its sheath.

The 4 remaining etiological factors are of lesser importance and frequency than trauma. Although they can initiate an attack, they are usually associated factors in the more severe attacks which are caused by trauma.

PATHOLOGY

The inflammatory process involves the tendon, as well as its bursa which surrounds it. Although a tendon was never sectioned, by analogy it may be inferred that all the inflammatory stages may be present, such as serous effusion, plastic exudate, fibrinous exudate, and adhesions. The tendon swells and loses its elasticity. Failure of the tendon to assist in the coaptation of the head against the glenoid cavity may lead to an outward dislocation. The tendon encased in a tight tunnel and pressed against arthritic deposits may gradually wear out, atrophy, and even disappear, in which case the remaining portion attaches itself into the bicipital groove. The muscles in and about the shoulder may atrophy.

SYMPTOMATOLOGY

There is pain along the bicipital groove, both subjectively and objectively. The subjective pains may be somewhat diffuse about the shoulder, but the objective pain *is always constant and always located in the bicipital groove.* It can be definitely elicited by pressure of the tip of the examiner's index finger upon the bicipital groove, especially when the arm is abducted and, thus, contrasts with the lack of response to pressure upon other points on the shoulder. If one is familiar with this situation, it enables the examining physician to foretell the exact location of the pain before examination. A patient is frequently intrigued by the fact that the examining physician is able to locate and outline the location of pain, without having previously examined the patient. The pain is superlative in quality in the acute cases. It is both diurnal and nocturnal, exaggerated by movements of the arm, or pressure upon the head of the humerus. The patient is unable to sleep and drugs have little or no influence upon the pain, except, perhaps, morphine in half grain dose. In most cases the pain occurs suddenly, occasionally it may be insidious.

Clinically, there are three distinctive types:

1. The acute type, characterized by violent pains in the "shoulder," both diurnal and nocturnal, little or not at all influenced by drugs.

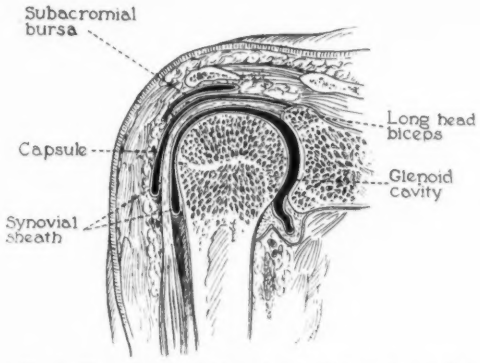


Fig. 2. Shows tendon of long head of biceps in relation to the joint, capsule, and humerus. (After Callander, *Surgical Anatomy*).

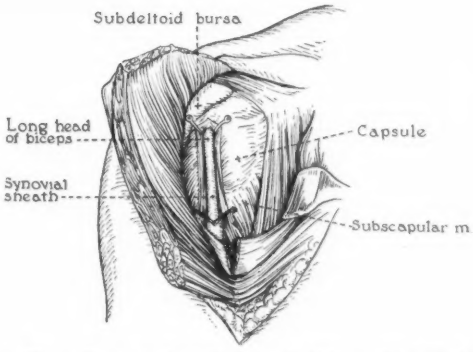


Fig. 3. Shows tendon of long head of biceps with synovial sheath split and reflected outward. (After Callander, *Surgical Anatomy*).

There is loss of shoulder function, because of pain. There is inability to raise, abduct, or place the arm against the back. Passively, the arm can be raised to the level of the shoulder, but not beyond that point. There is a *specific tenderness along the bicipital groove*. The pain lasts from a few days to a couple of weeks, when it gradually subsides, especially if diathermy has been used, or it may become subacute.

2. The subacute type, in which the pain is less severe, not so continuous, and may be paroxysmal, especially at night. There is some impairment of function and the patient learns to raise the affected arm with the opposite hand. The arm can be raised to the level of the shoulder and even beyond, although the movements are tolerably painful. The subacute type may be a continuation of the first type, or it may start as such in frank rheumatic cases. This second type may last from a few weeks to a few months, or it may merge into the chronic type.

3. The chronic type exhibits to a lesser degree all of the previous symptoms. The patients learn to fix the scapulohumeral structures and assist themselves in difficult movement with the opposite arm. There is more or less voluntary and involuntary fixation of the shoulder and there may be muscular atrophy present. This type may last indefinitely or be subject to either remissions or paroxysms.

Quite recently I have seen a patient who suffered from an acute attack of shoulder pain about 3 years ago. The condition had passed through all the three stages over a period of 9 months, and had left the patient with occasional pains in the shoulder, especially at night, and with inability to raise the arm much beyond the level of the shoulder. He was unable to place the dorsum of his hand against his back. Although his occupation required the use of a hammer, he learned to fix his shoulder and do all the work with his forearm and hand, using a short range of excursion, with the elbow as a pivot, instead of his shoulder. He was rather surprised when he realized that he had discarded the shoulder movements in his daily work and admitted that occasionally he raised his arm with the assistance of the opposite hand. The shoulder muscles were considerably atrophied. During a recent exacerbation, he had acute pain along the bicipital groove.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

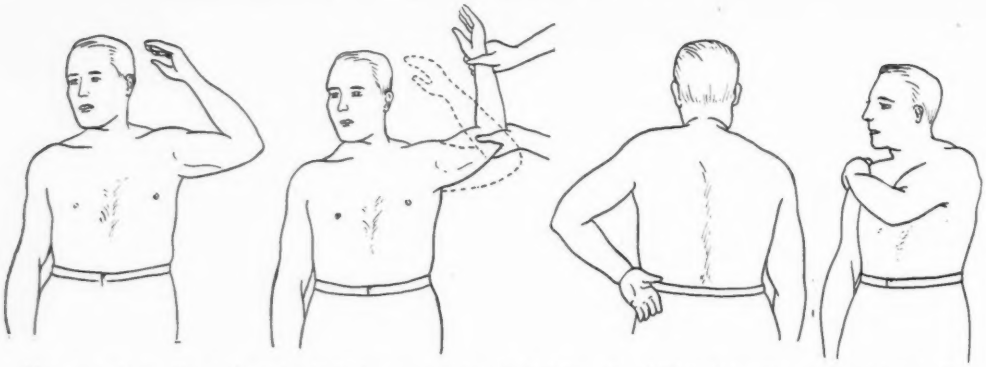
Since most of the articular and periarticular affections express themselves in terms of pain and limitation of motion, it becomes a diagnostic problem to establish with accuracy the exact tissue, or structure, which is responsible for the clinical picture.

Most of the conditions which tenosynovitis of the long head of the biceps humeri resemble are due to some injury. In this affection the character of the trauma is in the nature of a jar, or sudden pull upon the tendon rather than a single, violent blow upon either shoulder, or tendon.

True enough, patients suffering from tenosynovitis of the long head of the biceps humeri may be arthritics or rheumatics, yet this factor alone is not sufficient to bring about the clinical complex, trauma being a requisite or an important contributory factor.

Topographical pain along the bicipital groove is a pathognomonic sign in this ailment.

Inability of the patient to raise his arm above the level of the shoulder, to abduct it, or place



Figs. 4, 5, 6, 7. Fig. 4, 6, and 7 indicate movements which are limited and painful when attempted. Figure 5 shows in dotted line the extent of voluntary movement and in full line, the additional elevation with assistance. (Suggested to the artist by Pasteur's photographs in J. de radiol. et d'électrol.)

the dorsum of the hand against his back are likewise pathognomonic.

Table I is a presentation of the conditions which tenosynovitis of the long head of the biceps humeri may resemble.

PROGNOSIS

Mild and even severe inflammations occasionally subside within 5 to 6 days when properly treated and patient abstains from movements of the arm. The patient who is not in position to discontinue work, as well as the patient who remains without treatment, may suffer for several weeks and usually is a candidate for chronicity or recurrences.

The three types, already mentioned, may merge into each other, the time period of each varying in various individuals. On the whole, it may be said that when the cause is a mild trauma, or even a systemic, metastatic infection, the condition can be better controlled and temporized than when it is due to a severe trauma, especially in older, arthritic patients. Recurrences are occasionally seen; such recurrences, in reality however, are exacerbations of conditions which have abated but which have not entirely subsided. I have seen violently acute inflammations subside within a few days, while mild lesion passed on into the other phases.

TREATMENT

It is fair to state that the usual drugs which control or modify arthralgias, neuralgias, gout or rheumatism, have little or no effect upon tenosynovitis of the long head of the biceps and that there is no specific remedy for it. Morphine, in large doses, controls the pain, but is not capable of abolishing it entirely, as the slightest movement or jar of the shoulder will bring on pain, even with patient under the influence of morphine. Pasteur suggests ionization with salicylates, iodides, and atropine.

Much benefit and occasionally instant cure can be obtained by sudden traction upon the arm and shoulder while the arm is relaxed and in a position of abduction. The rationale of this treatment is based upon the supposition that the tendon does not fit properly in the groove and that the maneuver makes a satisfactory replacement in the groove. One may argue that since the biceps tendon fits snugly in the bicipital groove, it is difficult to conceive its displacement out of the groove. Sumner L. Koch commenting on the sudden relief of pain by sudden traction upon the arm in abduction states: "I am wondering if this may not be due to the tearing of adventitious adhesions rather than replacement of the tendon in its groove. As you well know, such manipulations constitute one of the helpful 'stunts' of bone-setters, and they frequently secure relief in this way for patients who had persistent pain and discomfort from constant pulling and irritation of adhesions which have formed in spaces lined with synovial membrane." On the other hand, E. L. Gilcreest, in an article entitled, "Dislocation and Elongation of Long Head of the Biceps Brachii," speaks of many cases reported from dissecting and postmortem rooms and "numerous others have been recorded as having been seen clinically, but not operated upon." A. W. Meyer dissecting one thousand arms found 50 cases of "marked dislocation of the tendon and many others of lesser degree." Gilcreest found no mention of any operative treatment for this condition in the

general literature. He states, however, that the condition can be corrected by manipulation or operation.

In the acute phase of tenosynovitis of the long head of the biceps, patient must rest in bed, placing the arm and forearm on 2 pillows in order to get some comfort.

Diathermy is the principal remedy, especially in the acute cases. This form of physical therapy induces hyperemia, which activates the blood supply, both superficial and deep. This, in turn, assists in the process of repair and promotes absorption of inflammatory exudates. It also maintains muscle tone and prevents atrophy. It should be administered daily from 30 to 60 minutes, preferably in the patient's home or in the hospital. I have found that patients who leave the office and come in contact with cold air do not fare well.

In the subacute stage, diathermy should also be used. However, if pain has definitely abated, gentle massage is recommended. Faradization of the tendon of the long head of the biceps is beneficial and should be administered either daily, or every other day, care being used to avoid muscle fatigue.

In the chronic cases, especially if there is muscular atrophy, massage, faradization, active and passive motion, in addition to diathermy, are definitely indicated. All forms of electrical treatment, such as high frequency, ultraviolet, infrared, carbon light and heat are beneficial and should be used in turn, the amount depending upon the relief the patient gets from their use.

Faradization diminishes pain and often allows patients to perform movements formerly impossible or painful. Galvanism is of value. Pasteur speaks of "rapid and remarkable success" in 5 cases by the use of high tension galvanism of weak intensity.

I advise my patients in the subacute and particularly in the chronic stage, to build a series of vertical shelves at a distance of 4 to 5 inches apart and instruct them to place the arm on these shelves. They start with the shelf which causes no pain, which is usually at the level of the deltoid. Then, they are asked gradually to reach higher shelves, daily, or several times a day, being guided by the absence of pain. The arm is kept on these shelves from 3 to 5 minutes. These exercises must not cause pain or tire the patient.

Potassium iodide is suggested in chronic cases

TABLE I.—PRESENTATION OF THE CONDITIONS TENOSYNOVITIS OF LONG HEAD OF BICEPS HUMERI RESEMBLES

Clinical entity	Etiology	Signs and symptoms	Function
Tenosynovitis long head biceps humeri	Trauma: sudden jar, or pull. Rheumatic tendency. Metastatic infections Climatic changes	Diurnal and nocturnal pains, uninfluenced by drugs. Topographical pain (bicipital groove) Afebrile	Inability to raise arm above level of shoulder, abduct, or place hand against back
Acute rheumatism	Definite etiology unknown (numerous contributory factors)	Polyarticular pains, often controlled by drugs Migratory pains Constitutional symptoms Febrile Diffuse local swellings, chiefly involving joints	Painful movements in any direction
Rupture of supraspinatus muscle	Blow upon the shoulder or strain with arm in abduction	Maximum pain over the tuberosity Pain, diffuse; shoulder weak Defect below and lateral to the acromion X-ray may reveal spicule of bone attached to tendon	Difficulty of raising and abducting arm
Rupture of biceps tendon	Trauma: old and arthritics Always in men Rare condition: D. E. McKenna: 85 cases; J. O. Rankin: 4 cases from general literature	Laxness and spheroidal bulge of muscle near elbow Head of humerus drawn upward and forward; false dislocation	Flexion and supination painful Abduction of arm limited (rupture of long head tendon)
Subacromial bursitis	Fall or blow upon apex of shoulder Occupational (painters, for ex.) Pressure upon shoulder by heavy objects	Pain, especially nocturnal extending up to neck and down on arm Fullness beneath deltoid Tender spot below and close to tip of acromion, disappearing on abduction (latter hides bursa	External rotation and abduction limited and painful; referred to insertion of deltoid X-ray: wider space between acromion process and head of humerus (contrasts with well side)
Subdeltoid bursitis	Fall	Swelling and fluctuation over tip of shoulder Pain: insertion of deltoid; bicipital groove Deltoid movements painful Muscular spasm (acute stage) Humerus approximated against scapula	Painful abduction and external rotation

SUMMARY

1. Tenosynovitis of the long head of the biceps is a new, yet definite, clinical entity.

2. F. Pasteur, medical colonel of the military hospital Val-de-Grâce, France, described the condition fully and clearly and should be given priority of record in medical literature.

3. The condition is the most common form of the periarthralgias of the shoulder (Pasteur).

4. Inability to recognize, appraise, and treat this condition adequately is responsible for invalidism, chronicity, and functional disability, which can be either improved, modified or cured, if properly diagnosed and managed.

5. The treatment is largely mechanotherapy and physiotherapy.

BIBLIOGRAPHY

1. CALLANDER, C. L. Surgical Anatomy, p. 792: 793. Philadelphia and London: W. B. Saunders, 1933.
2. GILCREEST, E. L. Ann. Surg., 1936, 104: 118.
3. LECLERCQ, J., and ROURESCO, A. Ann. de méd. lég., 1926, 6: 517–519.
4. MCKENNA, D. E. Surg. Clin. N. America, 1927, 7: 979–984.
5. MEYER, A. W. Arch. Surg., 1928, 17: 493–506.
6. PASTEUR, F. J. de radiol. et d'électrol., 1932, 16: 419–426; 1934, 18: 327–328. Presse méd. 1933, 41: 142–143. Gaz. d. hôp., 1934, 107: 477–479.
7. RANKIN, J. O. J. Bone & Joint Surg., 1933, 15: 1003–1006.
8. STEINDLER, A. Mechanics of Normal and Pathological Locomotion in Man, p. 292. Springfield, Ill., and Baltimore, Md.; Charles C. Thomas, 1935.

OPERATIVE INJURIES OF THE URETER

DAVID FEINER, M.D., Brooklyn, New York

INJURY of the urethra, bladder, and ureter continues to plague the gynecologic surgeon because of its frequency as a complication of pelvic operations. Of these, injury to the ureter is the most common and most serious. Various observers place the incidence of ureteral ligation as a complication in 1 to 3 per cent of all operations on the female genital organs. Although a fairly large number of case reports of operative injury of the ureter is revealed in a survey of the literature, it is very likely that most of the cases have never been reported and that many of these have passed unrecognized. Caulk and Fischer speak of the accident occurring much more frequently than is generally believed. Sampson, in one of the first comprehensive papers on ureteral trauma, claims that the injury, either in the form of ligation or clamping "is of common occurrence during gynecological work."

A notable presentation by Bland, in 1925, brought the literature up to that date. This paper included Herman's series of 24 bilateral cases, Barney's report on 63 cases, including 32 cases presented by Sampson in 1902, and a group of 159 cases presented by Oeconomes. Thus, Bland collected from the literature a total of 316 cases, and he himself gathered 125 additional cases from men active in abdominopelvic surgery. Nevertheless, he emphasizes the fact that, even with this large array of cases collected, it is probable that a large number of others have not been recorded, or have escaped recognition.

In addition to the 8 cases recorded herein, we have collected from the literature, both here and abroad, another group of 260 cases, which were reported from 1925 to 1936. This brings the total up to 710 cases, of which 109 were bilateral and 601 unilateral.

From the Gynecological Services of the Israel Zion and Beth Moses Hospitals, Brooklyn, New York.

TYPES, ETIOLOGY, AND RESULTANT EFFECTS OF URETERAL INJURY

Injury to the ureter may result from direct trauma, such as cutting (complete or incomplete), puncture, crushing by clamps, or by ligation. Occasionally, the wide dissection of the Wertheim technique leads to sloughing of the ureteral wall due to disturbance of its blood supply. In the majority of instances, ureteral injury is unilateral. Bilateral involvement of the ureters occurs in about one-sixth of the cases.

In clinics in which the radical abdominal hysterectomy for carcinoma of the cervix is performed, this operation is most frequently responsible for the occurrence of the accident. Vaginal hysterectomy is next in frequency. Abdominal hysterectomy was the primary operation in 4 of the 8 cases reported in this presentation. In 3 of them, the hysterectomy was performed for multinodular fibroid uteri, and in 2, the hysterectomy was complete. When chronic pelvic inflammatory disease distorts the anatomy during a hysterectomy for a fibroid uterus, or when cervical or intraligamentous myomas change the normal relations of the pelvic course of the ureter, the risk of injury is increased. Operations for intraligamentous tumors are especially prone to this complication. In 1 case of this series, the ureters were bilaterally involved during a Fothergill operation.

The result of accidental occlusion or injury of the ureters is governed by the location and extent of the damage.

The following summary by Robinson covers all eventualities:

A. Unilateral. 1. Section, followed by leakage and acute infection, either local or widespread.

2. Partial section with subsequent leakage and fistula formation, either uretero-abdominal or, and more likely, ureterovaginal.

3. Ligation, followed by atrophy of the kidney, with or without symptoms of renal inadequacy. In some cases, acute or chronic uremia.

4. Ligation with reflex suppression and complete anuria (1.6 per cent—Barney).

B. Bilateral. 1. Double section, followed by leakage, general infection and death.

2. Double ligation with anuria and uremia; fatal if unrelieved.

C. Partial occlusion or kinking from peri-ureteral adhesions following various abdominopelvic operations.

In the 260 cases collected from the literature during the period 1925–1936, unilateral injury occurred in 236 cases, as follows:

1. Radical abdominal hysterectomy for cancer	54
2. Total abdominal hysterectomy: (a) For uterine and cervical myomas or extensive pelvic inflammatory disease	48
(b) Ruptured uterus	1
3. Supracervical hysterectomy: (a) Indication not stated	26
(b) Complicated by chronic adnexal disease	18
4. Vaginal hysterectomy: (a) Cancer of cervix and portio (radical Schauta method)	13
(b) Prolapse	6
(c) Myoma	3
(d) Indication not given	13
5. Salpingo-oophorectomy: (a) Ruptured ectopic	5
(b) Ovarian cyst or adnexal disease	19
6. Operation for removal of intraligamentous tumors	19
7. Obstetrical procedures: (a) Extraperitoneal cesarean	1
(b) Forceps	5
8. One each of the following: inguinal herniotomy, incision and drainage of pelvic abscess, and operation for carcinoma of the rectum	3
9. Anterior colporrhaphy	2

CASE REPORTS

CASE 1. Unilateral injury—asymptomatic unilateral ligation. Mrs. N. H., aged 31 years. Previous operative procedure 4 years ago: left salpingo-oophorectomy for chronic tubo-ovarian disease. Patient was admitted to the Israel Zion Hospital, March 23, 1932, with complaint of pain in left lower quadrant of abdomen.

Pelvic examination revealed the uterus to be of normal size but displaced to the right by a tense cystic mass, which occupied the left lower quadrant. The impression was that of an intraligamentous cyst.

Operative findings: The left ureter had been ligated at the previous operative procedure, 1 inch from the bladder end, and the result was a huge hydro-ureter. The pelvic portion of the ureter was dilated to the size of an orange; the middle third of the ureter was dilated 1 inch in diameter, narrowing to one-quarter of an inch at the upper end. The kidney was atrophic, the size of a plum.

Procedure. The broad ligament was divided. The pelvic portion of the ureter, which was markedly adherent to the adjacent tissue, was exposed and separated by blunt dissection. The middle portion of the ureter was also exposed, by incising the posterior peritoneum, and freed from its adhesions. The entire ureter and kidney were removed.

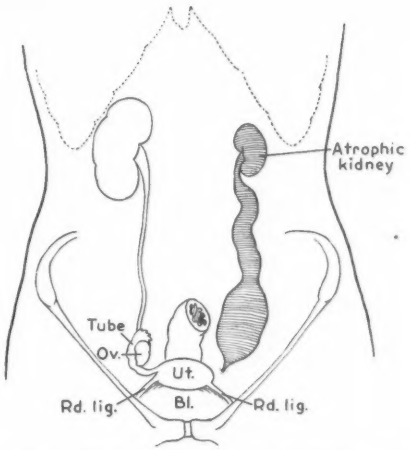


Fig. 1. Giant hydro-ureter resulting from accidental ligation of distal end of ureter. Case 1.

Convalescence was complicated by a vesicovaginal fistula which healed spontaneously. The patient left the hospital in good condition, within 3 weeks of the time of operation.

This case illustrates the fact that in many gynecological operations the ureter is tied, yet convalescence is uneventful and any symptoms produced by the ligation are easily obscured by other postoperative symptoms; thus the unilateral ligation goes unrecognized, with the ultimate result that the corresponding kidney dies. We are forced to the conclusion that many deaths, even when "suppression of urine" has been given as the cause of death following pelvic operations, are actually due to ureteral occlusion.

CASE 2. Ureterovaginal fistula treated by end-to-end anastomosis. Y. C., aged 43 years, was admitted to the Israel Zion Hospital, June 24, 1925. Primary operation, bilateral salpingo-oophorectomy, had been done 4 months previously. Eight days later, the patient began to dribble urine per vaginam.

The *cystoscopic* findings were as follows: Bladder capacity was normal, the bladder urine clear. Both ureteral orifices were normal except that the left one did not seem to function. The catheter could be passed up easily on the right side. On the left side the catheter met with an impassable obstruction 4½ inches from the bladder.

Operative procedure. A catheter was passed up the left ureter as far as the site of obstruction. An incision, 6 inches in length, parallel to, and about 0.5 inch above, Poupart's ligament, was made. The muscle was divided by blunt dissection, and the posterior wall of the pelvis was exposed retroperitoneally. After exploration, the lower end of the upper section of the severed ureter was isolated. It was found to be greatly distended, its caliber being about the

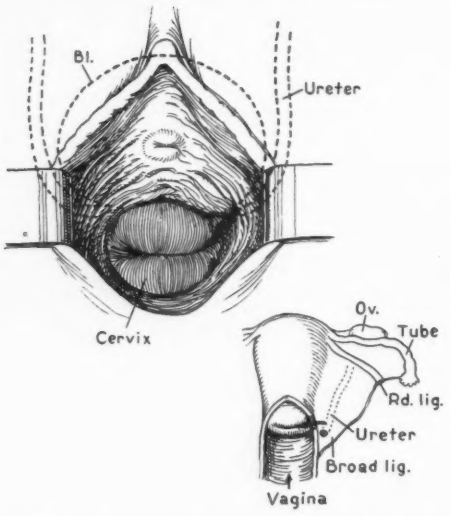


Fig. 2. Deep laceration through the left angle of the cervix, extending up into the broad ligament, and involving the distal end of the ureter. Case 3.

size of one's thumb. The lower segment of the ureter was found collapsed and hugging the ureteral catheter introduced from below. The two ends of the ureter were freed, and an end-to-end anastomosis was performed. The ureteral catheter was passed up through the point of union and on into the upper segment as far as the kidney pelvis.

The convalescence was smooth and urinary drainage via the catheter was adequate. The patient was discharged August 15, 1925. At that time the incision was healed except for a small opening, through which escaped a free watery-urinous discharge (persistent uretero-abdominal fistula). There was no evidence of vaginal leakage.

Bump and Crowe state that when ureteral anastomosis over a catheter is done the kidney pelvis should always be drained through a pyelostomy or ureterostomy above the line of repair. Had such prophylactic drainage been utilized in this case, the poor result obtained perhaps might have been avoided.

Case 3. Ureterocervical fistula treated by ureterovesical anastomosis. R. R., aged 31 years, was admitted to the Israel Zion Hospital August 25, 1924. Four months before admission, the patient had had a difficult forceps delivery of a dead fetus, with the result that there was a deep laceration through the left angle of the cervix, extending up into the broad ligament. This laceration apparently missed the uterine vessel, but involved the left ureter, as urinary dribbling followed immediately.

Examination on admission showed a thick scar in the cervix, extending up into the base of the broad ligament, and urine was observed escaping from the cervical canal.

Cystoscopic examination, with ureteral catheterization, revealed an impassable obstruction 1.5 inches from the left bladder orifice.

Operative procedure, August 27, 1924. An incision was made just above, and parallel to, Poupart's ligament on the left side. The ureter was identified and separated down to the level of its crossing the uterine artery. The ureter showed no evidence of dilatation, and the point of injury was apparently at that level. The distal end of the ureter was ligated. The proximal end was then implanted into the bladder through a small incision which had been made in the latter viscus, for this purpose.

In the week following operation the patient's condition was fairly satisfactory, except for a profuse seropurulent discharge of urinous odor, through the incision. For 2 weeks thereafter, the patient ran a septic temperature with drainage of pus and urine from the wound. On the twenty-first day after operation there was a profuse hemorrhage from the lower angle of the incision and the patient went into shock. She was taken to the operating room and the wound was explored. It was found that there was extensive retroperitoneal extravasation with free bleeding from a large vessel adjacent to the point of anastomosis. This vessel was ligated, and the wound was cleansed and packed with iodoform gauze. The usual shock treatment was instituted, including blood transfusion, but was unavailing and the patient expired 2 hours later.

Case 4. Ureterovaginal fistula treated by nephrectomy. S. G., aged 40 years. Hospital No. 2778. Patient was admitted to hospital with fibroid tumor of the uterus. Pelvic examination revealed an irregular, hard tumor mass, the size of a grape fruit, in the fundal portion of the uterus.

On November 25, 1921, panhysterectomy was done.

Urinary leakage was observed from the vagina on the second day after operation. The patient had a stormy convalescence for the next 4 weeks, during which time there was considerable discomfort in lower abdomen with intermittent temperature, varying from 99 to 103 degrees. Marked frequency and urgency of urination were also present.

The patient was re-admitted to the hospital March 12, 1922. At that time there still was a free leakage of urine from the vagina. Cystoscopic examination revealed that the "bladder now practically normal. Ureteral catheter passed without difficulty up the right ureter. On the left side, an obstruction was encountered about 1 inch or 1.5 inches from the bladder. The right ureteral orifice was excreting normally, with a good functional reaction in 3½ minutes. No urine was excreted on the left side."

On vaginal examination urine was observed escaping from the left upper angle of the vaginal vault. The impression recorded on the chart was that there was present a ureterovaginal fistula secondary to incomplete section of the ureter at the time of the original hysterectomy.

In view of the poor general condition of the patient, it was considered inadvisable to attempt ureteral anastomosis or implantation of the ureter into the bladder. Therefore, a nephrectomy was done March 16. Convalescence following nephrectomy was uneventful, all urinary symptoms gradually disappeared, and the patient was discharged April 15, 1922. The family physician reports that at present the patient is in fairly good health with no direct sequelæ resulting from her operative complication.

Case 5. Bilateral ligation treated by deligation. S. S., aged 33 years, was admitted to the Israel Zion Hospital, November 8, 1929. Following a curettage performed for incomplete abortion, the patient went into extreme shock. Accidental perforation of the uterus was suspected. At laparotomy, 2 hours later, the abdomen was found full of blood-clots from a tear involving almost the entire breadth of the uterus and extending into the left broad ligament. Hysterectomy was performed with marked difficulty because of continuous bleeding from retracted vessels, which

made it necessary to take deep bites with mass ligatures in order to control the bleeding. A transfusion of 1000 cubic centimeters of whole blood was given. Eight hours after operation, 12 ounces of urine was obtained on catheterization. No urine was voided in the following 24 hours, at which time it was determined by catheterization that the bladder was empty.

Cystoscopy was now done under local anesthesia. "Both ureteral orifices were congested, flaccid, gaping, with no visible peristalsis. No urine was seen coming from either ureter. Catheters could not be passed beyond 4 centimeters from the bladder on either side."

An immediate laparotomy was done. The previous midline incision was opened. Cystoscopy was done at the same time, with ureteral catheters in place. On the left side, the ureteral catheter was palpated at the point of obstruction, and the sutures in that region near the cervical stump were cut. The catheter was then introduced beyond the obstruction and urine began to flow. The same procedure was followed on the right side, but the obstruction was found near the base of the ovarian ligament. Urine also began to flow freely from this side. The abdomen was closed. Both catheters were left *in situ*. Convalescence was stormy, in spite of the fact that urinary secretion was adequate. The patient died on the fifth day.

Opinion. Sepsis, pneumonia, paralytic ileus.

CASE 6. A. S., aged 39 years, was admitted to the Beth Moses Hospital, January 12, 1933. A total hysterectomy for fibroid uterus and lacerated, eroded cervix was followed by complete anuria for 24 hours.

The general condition of the patient appeared good. The abdomen was soft. Her only complaint was nausea with occasional vomiting. No pain or tenderness was noted over either kidney region. She was taken to the operating room 24 hours after operation and cystoscoped. *Cystoscopy* showed the following: "Both ureteral orifices appear motionless; no urine is seen escaping from either orifice. Ureteral catheterization was attempted and both ureters were found obstructed 1 inch from the bladder end."

Operative procedure and findings. Immediate laparotomy was done through the previous incision. Although only 24 hours had elapsed since primary operation, the pelvic tissues were markedly thickened and edematous. The normal anatomy was completely distorted by a massive exudate which completely buried the cervical stump. The tissues on either side of the latter were separated by blunt dissection. The right ureter was isolated and found to be dilated to about the size of one's little finger. It was freed downward toward the bladder until the point of obstruction was reached. The offending ligature was found to be that which included the dense basal segment of the broad ligament on each side of the cervix, together with the vascular plexus adjacent to it. Both ligatures were cut with considerable difficulty because of the depth of the pelvis, the dense exudate, and the general oozing. The ureteral catheters, which had been previously passed through the cystoscope, were now advanced up on both sides to the pelvis of the kidney and urine was immediately excreted on both sides.

The postoperative reaction was poor; the patient was in moderate shock. She was transfused 4 hours later. She was catheterized and 14 ounces of urine was obtained. During the following 24 hours the patient excreted 60 ounces of urine. Her condition, nevertheless, gradually grew worse and she expired 36 hours after operation.

In explaining such mortalities, Barney has pointed out that the suppression of urine alone is not the determining factor. In neither of these cases was it long drawn out; as a matter of fact, the condition may exist for a much longer period of time before death ensues. Morris cites a case of anuria of 17 days' duration, while another surgeon with whom Barney corresponded, saw in consultation a patient who had passed no urine whatever for 23 days. Both these cases terminated fatally, but they serve as proof that the human system can sometimes offer good resistance to this particular onslaught. In the type of case under consideration, Barney ascribes the high mortality to other factors, such as severe and prolonged operation in a patient who is already below par and to whom the ureteral injury is merely the last straw. In our experience, deligation has proved a formidable operation which presents unusual technical difficulties. These are, chiefly, the extreme anatomical distortion, the extensive exudate, and the inevitable bleeding in the operative region.

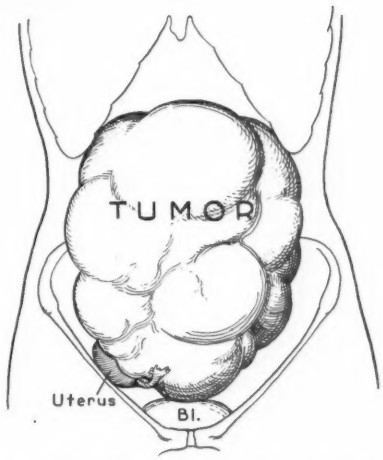


Fig. 3. Huge tumor mass, originating from the left intraligamentous fossa, occupying the entire abdominal cavity, and displacing small uterus to the extreme right. Case 7.

CASE 7. Bilateral ligation treated by nephrostomy. Case No. 65218, Mrs. A. J., aged 43 years, was admitted to the Beth Moses Hospital, September 20, 1934. Her chief complaint was intermittent vaginal bleeding and marked enlargement of the abdomen. The previous history was essentially negative, except for a cesarean section 7 years ago. Pelvic examination revealed a normal size uterus which was displaced to the extreme right by a tumor mass filling the entire pelvis. Abdominally, the same tumefaction, reaching up to the costal margin on both sides, could be palpated.

Operative procedure and findings. At operation, a huge tumor mass, which originated from the left intraligamentous space, displacing the uterus to the extreme right and

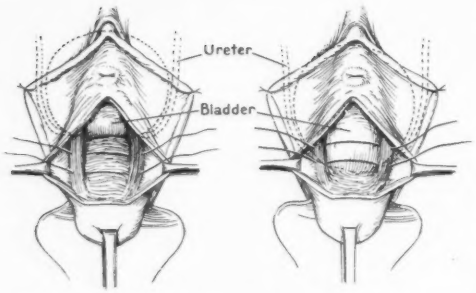


Fig. 4A, left. Fothergill operation with bladder and ureters mobilized and pushed above range of sutures. Case 8.
Fig. 4B. Fothergill operation. Bladder insufficiently mobilized, ureters within range of sutures. Case 8.

occupying the entire abdominal cavity, was found. The operative procedure consisted of supracervical hysterectomy and bilateral salpingo-oophorectomy, which was attended by great technical difficulties because of the unusual distortion of the anatomy. During the course of the operation, the bladder, which was densely adherent as a result of the previous low two-flap cesarean, was accidentally incised. At no time during the operation were the ureters visualized. The perforation in the bladder was repaired and a drain was inserted into the space of Retzius. At the end of the operation, a Pezzer catheter was introduced into the bladder *per urethram*. The immediate postoperative course was uneventful, except that no urine was expelled through the catheter. After 20 hours of anuria, it was suspected that the ureters had been occluded by ligatures.

A *cystoscopy* was performed and attempts to pass ureteral catheters up to the pelvis of the kidney failed on both sides. Both met with impassable obstructions about 2 inches from the ureteral orifices. Indigo-carmine injected intravenously did not appear from either ureter after 20 minutes.

A right nephrostomy was done at once. The kidney appeared large, hydronephrotic, and congested. A curved Kelly clamp was thrust into the pelvis of the kidney and a considerable amount of bluish fluid (urine discolored by indigo-carmine) gushed from the wound. A Pezzer catheter was inserted.

The patient was given a direct blood transfusion of 350 cubic centimeters and rallied immediately. For the first 48 hours there was very little secretion through the nephrostomy tube, but on the third day a flood of urine was excreted, saturating the bed. This profuse drainage continued until the eighth day after operation when bloody fluid of urinous odor was removed from the bladder by catheter. Drainage through the nephrostomy wound decreased to almost nil and the tube was removed on the twelfth day after operation.

The blood chemistry figures in this case were extremely interesting, showing enormous nitrogenous retention. On the second day after the nephrostomy, and before any urine had appeared, the urea nitrogen was 110 and the creatinine 10 milligrams. Two days later, with urinary excretion, the urea nitrogen was 76 milligrams and the creatinine 4.35 milligrams. Eight days later, the urea nitrogen was 17 milligrams.

On the twenty-fourth day after operation *cystoscopy* was done and again both catheters met with obstructions at the same level as before the nephrostomy, but the indigo-carmine was recovered from both sides within 5 minutes after intravenous injection of the dye.

The patient was discharged from the hospital on the thirty-fifth day after admission.

In retrospect, the question that arises in this case is whether the ureters had been ligated with catgut and the lumen restored as soon as the catgut was absorbed. It has been shown experimentally that plain catgut is not absorbed before the end of the third week, whereas this patient developed spontaneous restoration of ureteral function 8 days after the nephrostomy. It would appear that the obstruction in this instance may not have been due to encircling ligatures, but to kinking and inflammatory swelling, on the subsidence of which the ureters opened spontaneously.

CASE 8. Bilateral ligation treated by vaginal deligation. F. B., aged 56 years, was admitted to the Israel Zion Hospital, March 10, 1936.

Operative procedure. Anterior colporrhaphy, Fothergill method. The immediate postoperative reaction was good. However, during the following 24 hours, no urine was excreted through the retention catheter, thereby arousing the suspicion of the operator that both ureters had been occluded by the ligatures. At this time a cystoscopic examination revealed the following: "Right ureter identified, and showed marked edema and pouting. All attempts to pass a ureteral catheter into the orifice were unsuccessful, due to edema. The same condition was found on the left side. It is believed that the edema is secondary to ligation of the ureters higher up. Following intravenous indigocarmine, no dye appeared in the bladder after 30 minutes."

An immediate deligation from below was decided upon. The repaired anterior perineal wall was reopened, and the superficial sutures were incised, the three interrupted sutures approximating the lateral pubocervical tissues (bladder pillars) being laid bare. All three sutures were cut, thus revealing the uppermost of the three to be the culprit. The area thus freed was packed with iodoform gauze and the mucous membrane approximated with continuous locked sutures of chromic catgut. A cystoscope was then introduced into the bladder, and a No. 4 F. catheter met with obstruction on both sides, about 4 centimeters from the bladder (probable point of ligation); with great difficulty, this obstruction was overcome, and both catheters were passed up to the level of the kidney pelvis; urine immediately returned from both sides, and it was tinged with the blue dye; the catheters were left *in situ* for drainage. In the next 24 hours, 32 ounces of urine was excreted through the catheters. The ureteral catheters were then removed and the patient was catheterized at intervals of 6 hours for the next 5 days. On the seventh day after operation, the patient voided spontaneously, and from that time on the convalescence was uneventful.

Fortunately, this type of injury as a complication of anterior colporrhaphy is extremely rare. This is confirmed by a personal communication from Dr. William Fletcher Shaw, of Manchester, who writes: "In this city we do some hundreds of this operation every year and have done so for the last 30 or 40 years, and I have never known a case in which even one ureter was tied. I can only suggest that this accident occurred because: (1) the

TABLE I.—UNILATERAL INJURY TO URETER

I.	Fistula (causative injury not stated):	
	A. Ureterovaginal	91
	B. Uretero-abdominal	8
	C. Combined ureterovaginal } Uretero-abdominal }	1
II.	Severed	55
III.	Resection	13
IV.	Ligation (One nephrectomy 8 years later for hydronephrosis)	18
V.	Clamped	10
VI.	Interference with blood supply	6
VII.	Partially severed	13

bladder was not sufficiently separated from its attachment to the cervix and pushed out of the way, or (2) that one of the sutures was inserted above the level of the reflection of the bladder. In cases in which the bladder seems to be very low I sometimes try to palpate the ureters, but I have never found any case in which they were inserted sufficiently low to be endangered by these deep sutures."

In the 253 cases assembled from the literature, unilateral injuries have been summarized in Table I.

The treatment of this group of cases is illustrated by Table II.

Bilateral injury of the ureters was present in 24 cases. These occurred as complications of the following operative procedures: radical abdominal hysterectomy for carcinoma, 13; radical vaginal hysterectomy for carcinoma, 1; complete hysterectomy for fibroid or pelvic inflammatory disease, 8; bilateral salpingo-oophorectomy for chronic adnexal disease, 2; Percy cautery operation for carcinoma of the cervix, 1.

Bilateral ligation of the ureters occurred in 11 cases; of these, 6 patients were treated by deligation; in 1 case, in which the interval was 48 hours, patient recovered but required a subsequent nephrectomy. Patients in the 5 cases remaining, deligated on the third or fourth day, died. Five patients in whom both ureters had been ligated were treated by nephrostomy. Of these, 2 required subsequent end-to-end anastomosis, 1 necessitated a secondary nephrectomy, and 1 a subsequent implantation of both ureters into the sigmoid. Four of these patients recovered and 1 died. In 1 case of bilateral ligation, no operative procedure was resorted to for relief of the obstruction, and death occurred on the fourth day.

There were 12 cases of bilateral ureterovaginal fistula; of these, 5 closed spontaneously; 3 were successfully treated by colpocleisis. In 3 cases, bilateral ureterovesical implantations were performed with a satisfactory result in all. One patient, on whom a Percy cautery operation had been done, developed gradual obstruction of both ureters, necessitating implantation of both ureters into the bladder. In this case the ultimate outcome was not stated.

TABLE II.—UNILATERAL CASES

Secondary operation	Number of cases	Recovered	Failure	Deaths	Third operation
1. Ureterovesical anastomosis	61	38† + 4 = 42	14 + 2 = 16	1	Nephrectomy (7 cured, 2 died)
2. Uretero-ureteral anastomosis	23	17	3	3	..
3. Nephrectomy	39	37	..	2	..
4. Nephrostomy	3	1	..	2	..
5. Ligation	19	15	2	1	Nephrectomy 1 (cured)
6. X-ray treatment for fistula	20	13	7	..	Nephrectomy 2 (cured)
7. Mackenrodt operation (ureterovesical implantation vaginal approach)	9	5	3	1	Nephrectomy 2 (cured)
8. Ureterorrhaphy	5	3	..	..	Nephrectomy 2 (cured)
9. Ureter implanted in sigmoid	2	1	..	1	..
10. Coagulation of ureteral orifice in bladder	1	1	..	..	..
11. Ureter anchored to abdominal wall	1*	..	..	..	..
12. Splint with catheter	4	3	1	..	..
13. Spontaneous healing without second operation.	22	13 + 9§	..	..	..
14. No operation	8	..	..	3# + 5 = 8	..
15. Ureteral catheterization	13	10	..	..	..

*Autonephrectomy.
†Fair-moderate stenosis.
§Dead kidney.
#Sepsis.

TREATMENT

If at the time of operation it is discovered that one or both ureters have been ligated or included in a clamp, the proper treatment is to deligate or remove the clamp promptly. Ordinarily, the ligature around the ureter, or instrumental trauma of the latter, is not sufficient to cause permanent damage. If, however, there is evidence that the vitality of the ureter has been so impaired that a fistula is likely to develop, immediate repair

should be done, in the form of uretero-ureteral or ureterovesical anastomosis.

Where both ureters have been ligated and it is not discovered until the following day or later, the condition is a serious one. The combination of complete anuria and threatening uremia makes immediate surgical intervention imperative. The three alternative procedures to be considered are: deligation of the ligated ureter, nephrostomy, ureterovesical anastomosis.

CONCLUSIONS

1. From the large number of cases of ureteral damage recorded in this paper, it is evident that the accident is a surgical complication far more common than is generally assumed.

2. It is quite likely that a certain number of unilateral ligations occur during the course of pelvic operations which are not recognized and which do not provoke immediate symptoms, with ultimate autonephrectomy on the corresponding side.

3. This accident may be sustained during any pelvic operation, but it is more common following radical abdominal or vaginal hysterectomy and notably in operative procedures for the removal of intraligamentous tumors. In selected cases in this group, catheters may be inserted into the urethra before the operation is started, as an additional safeguard.

4. The majority of cases are those of unilateral injury; more rarely, both sides are involved, the proportion being 6 to 1.

5. As an index of the seriousness of ureteral injury may be mentioned the mortality figures quoted by Bland of 33.3 per cent for the bilateral, and 18.8 per cent for the unilateral cases.

6. The most common sequelæ of ureteral injury are vaginal and abdominal fistulas.

7. If the ureter is divided during the course of a hazardous or markedly prolonged operation, the operator may be compelled to resort to ureteral ligation; but this is justifiable only when the risk of reparative procedure for the restitution of function of the injured ureter appears too great.

8. If a ligature or clamp has been placed on either one or both ureters, and the injury is detected at the time it is inflicted, and there is evidence that the vitality of the ureter has been so imperiled that fistula is likely to develop, immediate repair should be done in the form of uretero-ureteral or ureterovesical anastomosis.

9. In the case of bilateral occlusion, discovered after operation, with imminent danger of uremia, immediate deligation is the operation of choice, provided the patient's condition is such that she can endure this hazardous and time-consuming operation.

10. Nephrostomy may be the most feasible procedure when intra-abdominal work is contraindicated by gravity of patient's condition. This drainage should preferably be bilateral.

11. In view of our results of 100 per cent mortality with two intra-abdominal deligations, the writer feels that nephrostomy with subsequent operation for ureteral anastomosis or bladder implantation, when found necessary, is a much safer and, therefore, a preferable procedure.

12. Finally, the operator, when confronted with a damaged ureter, should be prompted in his selection of the reparative procedure with the fundamental aim in mind of the preservation of both ureteral and kidney function.

The author is indebted to those members of the staff who permitted him to utilize the records of their private patients as part of this study; and he gratefully acknowledges the co-operation of Dr. Maxwell Dorr and Dr. Harry Ehrlich for their assistance in assembling the preliminary data. He also desires to express his appreciation of the assistance given him in the completion of this survey by the Literary Research Department of the American College of Surgeons.

BIBLIOGRAPHY

1. Barney, J. D. Intraperitoneal division of one ureter Ann. Surg., 1910, 51: 362.
2. Idem. The effects of ureteral ligation. Surg., Gynec. & Obst., 1912, 15: 290–295.
3. Bland, P. Brooke. The treatment of accidental occlusion of the ureter. Atlantic M. J., 1923, 27: 341–351.
4. Bump, W. S., and Crowe, S. M. Uretero-ureteral anastomosis. Surg., Gynec. & Obst., 1929, 49: 346–351.
5. Caulk, J. R., and Fischer, R. F. Experimental study of the effect of ureteral ligation with particular reference to its occlusion during pelvic operation. Tr. Am. Ass. Genito-Urin. Surg., 1915, 10: 72–81.
6. Idem. An experimental study of ureteral ligation: demonstration of late results to ureter and kidney. Surg., Gynec. & Obst., 1920, 30: 343.
7. Herman, Leon. Unilateral ureteral injuries. Surg., Gynec. & Obst., 1923, 37: 756.
8. Idem. Accidental bilateral occlusion of the ureter. J. Urol., 1923, 9: 151–179.
9. Robinson, A. L. A note on injuries to the female ureter. Brit. M. J., 1921, 1: 665.
10. Sampson, John A. Ligation and clamping of the ureter as complications of surgical operations. Am. Med., 1902, 4: 693–700.

THE ALBEE SPINE FUSION OPERATION IN THE TREATMENT OF SCOLIOSIS

FRED H. ALBEE, M.D., Sc.D., LL.D., F.A.C.S., and ALEXANDER KUSHNER, B.Sc., M.D.,
Venice, Florida

IN SPITE of the many years it has challenged the ingenuity of orthopedic surgeons, the treatment of idiopathic scoliosis is still on an uncertain basis in many centers. The number of failures encountered in consultation practice and the variety of therapeutic procedures devised confirm this conviction. The problem of scoliosis has been characterized as one of the stumbling blocks of the orthopedic surgeon. In attempting to unearth the causative factors in this situation, the senior author feels that a critical survey of the therapy of scoliosis is warranted. The extensive experience gained in the operative treatment of diseases and deformities of the spine during a period of more than 25 years forces him to indict certain therapeutic regimens as having unsound bases. Many of these cases were especially instructive because of previous abortive attempts at treatment, particularly the injudicious employment of braces and plaster jackets. Their application seriously interferes later with a satisfactory realinement of the spine by surgical means. Unfortunately, the offending structures in early idiopathic scoliosis,—the muscles, tendons, and ligaments—are weakened by suppression of the stimulus of function. It must be realized that in treating curvatures with a brace, one attempts to correct the spine indirectly through pressure on the thorax. The ribs are elastic structures and a great deal of the force exerted will be merely spent on increasing their angulation, or changing the relations at the costal vertebral joints. When the brace is removed, the spine collapses, as Whitman aptly put it, like an abandoned accordion. Obviously, to remove the brace is to court disaster and both patient and the physician will cling to it like the proverbial drowning man. Figure 3b is illustrative of such a catastrophe. Figure 1, patient A.N., reveals rapid progress of curvature after 1 year in a plaster jacket. Furthermore, the utilization of a brace in a mild case will often weaken the soft structures, increase the angle of deviation, and set up a vicious cycle converting a non-progressive spine to one requiring operative correction.

From the Florida Medical Center, Fred H. Albee, medical director.

Treatment by corrective medical gymnastics is rational therapy in early idiopathic cases. Curvature is overcome by strengthening, not undermining, the mainstays of the spine. Early nonprogressive cases are easily eliminated. Our position in regard to operation is this: Corrective medical gymnastics without braces are carried on with periodical check up by trunk x-rays, which we find the most trustworthy method of recording the lesion. As soon as it is realized that the spine shows a tendency to increasing deformity, in spite of conservative treatment, operative stabilization of the spine is recommended. In the early days before the employment of the bone graft, such cases were almost a "nightmare" to the surgeon as he was compelled to see the most pronounced deformities develop right under his eyes and his hands were completely tied as to prevention. The operative treatment has proved a great satisfaction.

The Albee extra-articular arthrodesis as first conceived in 1908, was evolved from fundamentally sound biomechanical and physiological principles. That these were correct was attested to recently by the appearance of a patient whose spine had been fused a quarter of a century ago. He is pursuing an active and useful life today, as first officer on a transatlantic steamer. Although the profession was quick to adopt the operation in the treatment of Pott's disease and abandon conservative therapy, there has been a marked hesitancy to follow a similar course in the therapy of scoliosis. Steindler (7), after a large practice states, "In the light of the experience made with all methods of scoliosis treatment, one is justified in saying that operative fusion, while at this time accepted as a temporary solution, does not entirely solve the problem. In the advanced deformities of non-compensated cases, it will be the only refuge, and we owe a debt of gratitude to those who have developed the method and perfected its technique." This apparently sums up the attitude of the profession in general.

At the Florida Medical Center where the Albee fusion is the treatment of choice, most encouraging results have been obtained in the maintenance of correction. Maximum correction is

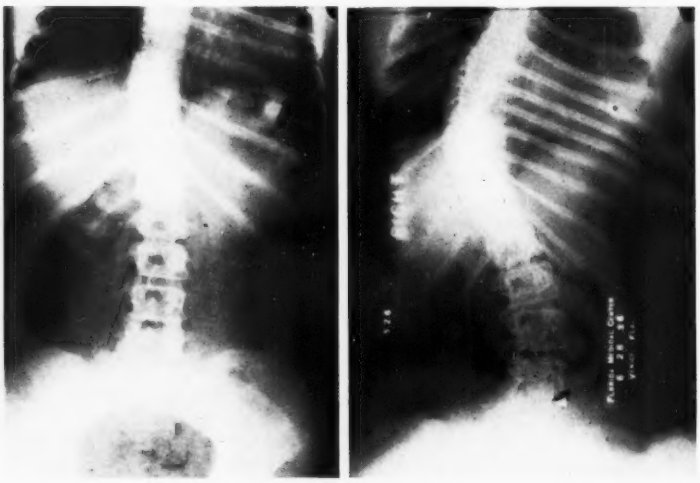


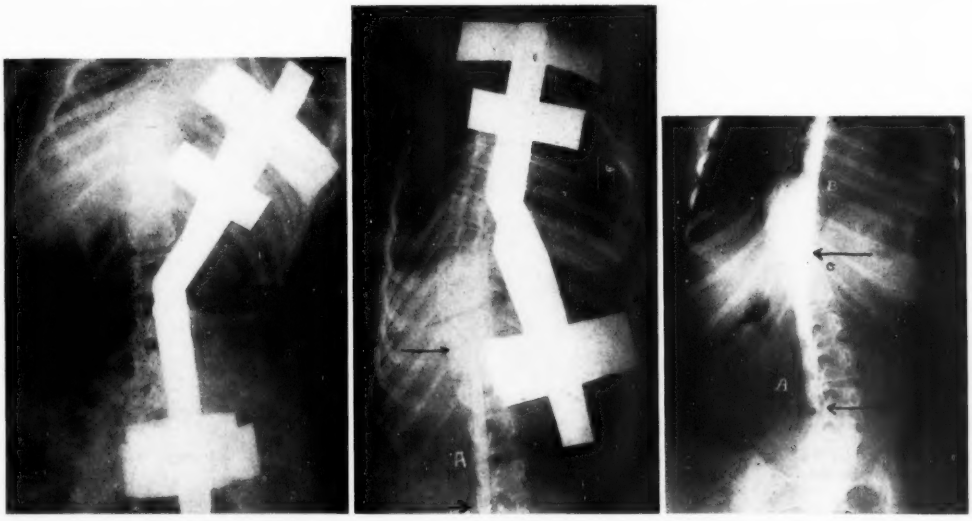
Fig. 1. a, left. Patient A.N. Idiopathic scoliosis. Spine at onset of treatment. b, After wearing plaster-of-Paris jacket constantly for 1 year.

obtained by the Risser cast. Operation is performed through a window cut through the plaster cast over the area of primary curvature to be fused. The cast is retained for 3 months and physiotherapy is then instituted. If the area of spine involved be extensive, then a second cast is applied, correction is accomplished with a turnbuckle, and a second bone graft is inlaid into the secondary curvature. Thus in early cases, arrest may be reached in 4 months, and in decompensated spines in 8 months. Except in the most advanced ones, if the primary curve is fused then, the secondary responds to the correction. Control of the primary is usually sufficient; second operation is necessary in only about 10 per cent of cases.

Figure 2 illustrates the various procedures. The lower pole of graft *B* was interlocked with the upper end of *A* at *C*, welding the unstable chain of articulations into a solid bar of bone. An increase in height of several inches is often noted as a result of "opening up" the curve with turnbuckle and hinged cast before operation. This method of realinement by an eccentric hinge and turnbuckle brings a powerful force to bear upon the curvature. Jackets designed to apply corrective compression to apex of curve are constructed contrary to the engineering principle of the keystone constituting the strongest part of the arch.

THE PROP GRAFT

Patient E.P. presented an interesting problem in treatment. Her curvature was of such a degree that her ribs had telescoped into the pelvis, producing painful symptoms with locomotion (see Fig. 3 a and b). The soft structures on the concave side had so contracted after prolonged conservative therapy that it was found impossible even by applying excessive force with the turnbuckle to secure a satisfactory correction. Accordingly, it was decided to extract the ribs from the pelvis at operation and prevent their prolapse by interposing a stout prop bone graft between the ilium and tenth rib to augment the spinal inlay graft with cross grafts at central portion of curvature (see Figs. 4 and 5). The prop graft must be carefully mortised into the tenth rib, as shown in Figure 5, to prevent it from slipping past into the pleural cavity. The graft is tunnelled through muscle planes as it is always desirable to provide for an adequate blood supply. Grafts should never be placed in an avascular environment such as fat or scar tissue. During convalescence, the patient displayed excessive zeal in developing her musculature and fractured the strut graft. Happily, a pseudarthrosis developed at the fracture site (*A*, Fig. 4), and thus there resulted a new articulation in the evolution of man. This structure permits articulation between the ilium and thoracic cage and removes any restriction of motion that absolute fixation may have occasioned. It is in this type of spine that the bone graft meets its supreme test, and to judge its worth one has only to listen to the enthusiastic comment of patients and parents.



a b c

Fig. 2. a, Same as Figure 1. Correction of lumbodorsal curve with turnbuckle and hinged cast. Turnbuckle not visualized. Compare with Figure 1b. b, Roentgenograms showing permanent fusion of lumbodorsal spine by means of bone graft, *A*, to prevent recurrence. Correction of dorsal curve by turnbuckle. Patient ready for second Albee fusion. c, Roentgenogram taken 5 months after second fusion operation. The lower pole of graft *B* was interlocked with upper pole of graft *A* at *C* so as to abolish articulation, construct an unyielding bony ridge, and as well to insure permanent correction. Note hypertrophy of graft *A*.

That the graft retains its vitality is proved by its permanency in cases of over 18 years' duration. To those clinicians who regard the graft as an osteogenetic scaffold for osteoblasts to make their way from ilium and pelvis and meet in the center, we would point out there is no confirmation—clinically or experimentally—for such a stand. The graft retains its vitality and advertises this fact by its ability to produce callus when fractured, or enter into the formation of pseudarthrosis as noted in Figure 4.

The routine employment of spine fusion without a tibial graft in early cases has been opposed chiefly because of the magnitude of the operation and the uncertainty of fusion. We admit that these criticisms are justified after noting that Brogden reports failure of fusion in 47 per cent of patients operated on at the Hospital for Ruptured and Crippled when done according to the Hibbs method. Steindler (7) reports "the so called break or false motion in a fused spine is very frequent" after the Hibbs fusion. Gaenslen remarks "to those who have done the Hibbs operation, it will be quite apparent that it is a difficult matter to get anything like a continuous periosteal tunnel by denudation of the lamina. . . . It is extremely difficult to carry out fusion on one side, especially when one considers that just one break in the operative procedure, such as missing a single set of articular facets, may jeopardize the entire operation."

With such poor results from the hands of competent orthopedic surgeons, there can be no doubt that the Hibbs operation is unsuited for scoliotic spines. The chain of arthrodesed articulations is no stronger than its weakest link. When marked rotation of the vertebræ has occurred, many of the articulations are inaccessible. The mechanical basis of the operation is incorrect. Fracture of the spinous processes tends to encourage further flexion and rotation. The center of gravity passes anterior to the bodies of the vertebræ in the dorsal region and the tendency of the spine to forward flexion is counteracted by ligamentous structures attached to the spinous processes—the ligamenta interspinale and supraspinale. Furthermore, there are important muscle attachments to this structure—the multifidus, semispinalis, and sacrospinalis groups. Denuding and fracturing the processes, by releasing the favorable action of these ligaments and muscles tends to encourage rather than correct further

Fig. 3. a, left, Patient E.P. Idiopathic scoliosis. Spine at onset of conservative therapy. b, Corkscrew spine after prolonged treatment by corrective exercises, braces, plaster jackets, and traction.

deformity. Complete immobilization is disturbed by the slight motion transmitted to the vertebræ by the costovertebral ligaments during the respiratory excursion of the ribs. The extended period of postoperative traction on a Bradford frame followed by plaster cast and brace for 1½ years does not invite recourse to surgery. A minor point, but of clinical importance, is the fact that the x-ray picture may not be of any assistance in determining whether or not fusion has been obtained. The superimposition of the shadows of potential areas of arthrodesis make this unlikely. Figure 6 is a case in point. The patient had been subjected to a Hibbs fusion and complained of pain with inspiration and motion —where none had previously existed. The x-ray film did not furnish any clues as to the localization of the pseudarthrosis, which was subsequently disclosed at operation. A tibial graft was inlaid at the break, and complete relief was obtained. The authors wish to tarry upon this as an undisputed fact,—that presence of pain is indicative of interruption of fusion. Pain is associated with muscle spasm when fusion has been attempted and failed. This superadded spasm tends to increase deformity. In other words, the *modus operandi* of the rapid increase of the distortion is due to induced pain and its resultant muscle spasm upon an unbalanced musculature. Finally, the operating time of 1 to 1½ hours is a major drawback when one considers the paucity of reserve that some of these patients possess.

The Albee operation offers a technique calculated to encourage corrective biomechanics and mobilizes the maximum osteogenicity of vertebral bone. The tibial graft is an active osteogenetic brace which re-enforces itself by proliferation of bone at points of greatest stress, according to Wolff's law. In regard to this an interesting phenomenon has been observed. We have noted that, when the graft was implanted nearer the tip of the spinous process, fusion occurred earlier and proliferation of bone was greatest. This is entirely in keeping with the mechanics of the operation. The spinous process is the arm of a lever the fulcrum of which is the intervertebral articulation. Therefore, the tip of the process is subject to the maximum stress or vice versa, the greatest corrective effort should be applied at the greatest distance from the fulcrum, i. e., at the tip. Practically, this is not always possible. However, the potential leverage of the spinous process is almost always available and is utilized to its maximum extent in the Albee operation.

A study of the trabecular system of a vertebra will elucidate this conception (Fig. 7). Translated into mechanical terms, the significance of these systems is as follows: The vertebræ manifest a more passive function in the body and a more active function in their processes.

Fig. 4. Same as Figure 3. Four years after operation showing bone graft holding securely the corrected position of ribs after they were extracted from the pelvis at operation. Union with tenth rib at *A*. Note increased density of tenth rib—also hypertrophy of spinal graft. Full correction not attained because of extreme contracture of soft tissues on concave side following extended conservative therapy. This patient indulges in the most strenuous of exercises, including skating and tennis.

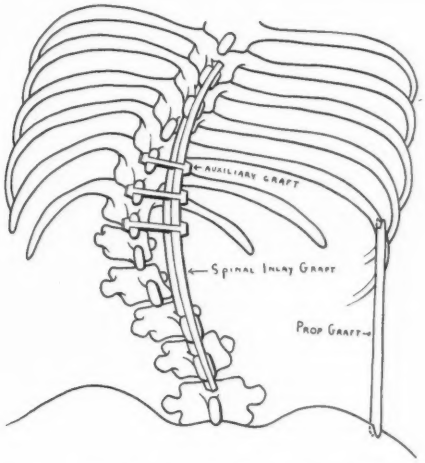


Fig. 5. Schematic representation of prop graft (Fig. 4). Note interlocking of graft and tenth rib, also auxiliary grafts at right angle to spinal graft, necessary in extreme degrees of curvature.

The body principally sustains pressure while the apophyses or processes are levers for the application of muscle force. Thus, when the process is fractured at its base, important ligamentous and muscular tension stresses are disturbed, so that the fusion obtained is unable to cope with the severe strain of the superincumbent weight and pseudarthrosis will result in almost 50 per cent of fusions attempted in the lumbodorsal region, in spite of the supporting brace (Steindler).

The graft should cover 7 to 8, or sufficient vertebræ so that the upper and lower poles will contact processes the vertebræ of which have not rotated to the degree present at the apex of the curve. In this way, a forceful derotating as well as straightening influence will be exerted on the intermediate vertebræ, and a corrective force brought to bear directly on the vertebræ. In contrast to the insertion of the graft for purely anteroposterior curvatures such as Pott's disease in which the graft is put in edgewise, it is important in this instance to put it into the split spinous processes and their embedding ligaments flatwise, so that its maximum strength can be used as an internal lever and splint still further to force the spine into alinement beyond that secured by the turnbuckle plaster jackets. We regard this as an outstanding feature of the operation. In extreme degrees of curvature, it may be necessary to shortcut several vertebræ because of the impossibility of obtaining a graft of sufficiently acute curve. They may be controlled by placing several auxiliary grafts at right angles from the main graft to the spinous processes of the central vertebræ into which the main graft cannot be inlaid because of inadequate curvature. In this instance, the spinous processes are split longitudinally but crosswise to receive one end of the auxiliary graft while the other ends are contacted with the main graft. This was necessary in our patient, E. P. (Figs. 4 and 5). The graft functions as a prop in this type of case and tends to be compressed between the bases of the arch. This is a favorable stress for the graft and maximum proliferation occurs.

An analysis of the divers stresses and strains that the graft is subjected to in different areas of the spine and its response to these offers an interesting study. Our investigation along these lines will be published at a later date.

The inferior osteogenicity of vertebral bone was demonstrated by Albee (1) in 1908, by animal experiments. This is readily confirmed by the surgeon who relies entirely on such bone for fusion. Furthermore, it will become quite evident when the statistics concerning the failure of repair of vertebral fractures are studied, and particularly those of the transverse processes. Although lying wholly within muscle, when broken and not displaced, they unite in less than 5 per cent of cases. Spies states, in his studies of

Fig. 6.

Fig. 8.

Fig. 9.

Fig. 6. Non-fusion in spine after Hibbs operation, demonstrating difficulty of localizing break. Onset of pain which did not exist before operation indicated failure of fusion—confirmed at operation. In three locations fusion had failed to take place but roentgenograms failed to disclose interruptions of fusion for the reason that the shadows of the bony elements were superimposed upon each other.

Fig. 8. Patient R.H. Excellent visualization of graft in lateral roentgenogram. This is of considerable aid to the surgeon in evaluating the progress and permanency of bony fusion.

Fig. 9. Patient L.A. This roentgenogram taken 24 years after the spinal graft was inserted has not yielded to the early tendency to progression—convincing evidence of the permanent corrective influence of the tibial graft.

an extensive number of cases of fractured articular processes, that they practically never unite. Likewise, the progress of union in fractures of the spinous processes is very poor. Willis has offered an embryological explanation. He states that vertebral bone together with the cerebrospinal system is derived principally from the ectoderm and that ectodermal tissue, such as spinal nerves, have a low degree of reparative potentiality. This is a distinct contrast to mesodermic tissues, such as skeletal bones, including the tibia, which exhibit a high degree of osteogenesis.

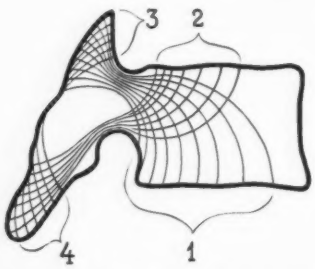


Fig. 7. Architecture of vertebra illustrating different and distinct systems of trabeculæ. The graft is inlaid and exerts its stress through system 4, thereby obtaining maximum leverage and corrective influence. (After Gallois and Japiot.)

Because of this inadequate callus forming capability of vertebral bone, it is clear that in order to secure a strong fusion, a single graft from a long bone of high osteogenicity should be used to supplement that of the local vertebræ. The tibia, fortunately for the purpose of the reconstruction surgeon, inherently has not only great osteogenetic potentiality and excellent reparative power but great strength. When inlaid into the spinous processes, it not only serves as an excellent corrective internal immobilization splint, but immediately fuses, by its own osteogenetic influence and that of the spinous processes themselves, with the spinal column. When one considers the wide limits of variations inherent in different individuals in regard to vertebral osteogenicity, it becomes incumbent upon the surgeon

to play the game as safely as possible and select not only an ample amount of bone in the form of a complete splint, but bone of the greatest known osteogenetic potentiality. To rely on the low osteogenetic potentialities of vertebræ, particularly in the form of chips, is to gamble on getting a favorable outcome instead of being practically certain of it (2).

In analyzing the vertebral bone chip operation, we mentioned the difficulty in following the progress of fusion by means of the x-ray picture. After the tibial bone graft operation, the x-ray is invaluable in this respect. Figure 8 demonstrates the excellent visualization of the bony bridge.

An important consideration when deciding treatment is the length of time required for an operation and the shock occasioned by it. An operation that consumes little time and induces comparatively little shock may obviously be undertaken when the surgical resistance of the patient is not of the best. The bone graft operation has been completed in as little as 9 minutes, in a favorable case of Pott's disease, if one's operating team is thoroughly familiar with the routine and the special instruments used. The technique does not require excessive retraction and there is no necessity to operate more or less blindly in regions difficult of access (3).

Postoperative care consists of 3 months in the turnbuckle cast, followed by physiotherapy. In severe cases, a modified Knight spinal brace is fitted and utilized until the x-ray discloses a firm bony bridge of large diameter.

Modifications in the method not in accord with these principles diminish its efficiency and unjustly bring it into disrepute. It cannot be satisfactorily combined with the Hibbs technique because the spinous processes should not be cut off. Osteoperiosteal grafts are too frail to obtain any immediate immobilization. Heterogenous grafts are biologically unsound and are to be condemned. In the series quoted above, Brogden reported non-fusion in 66 per cent of patients operated upon according to the Hibbs method, re-enforced by beef bone grafts. Rib grafts do not have the osteogenicity of the tibial grafts and do not lend themselves to being shaped as the strength depending on the thin cortical tubular form is lost. Their structure is too elastic to be able to exert the proper stress required.

Preston, after a careful study of the literature, comments: "It is evident that some form of operative treatment is thought necessary for all cases which cannot be easily controlled by exercise. Widespread dissatisfaction with the results of fusion operations which do not utilize some form of internal splint is shown by the large number of new procedures reported, most of which are modifications of the Albee technique. Many of them are mechanically unsound because either the firm anchorage of the graft is destroyed or the internal splint itself is composed of a substance which soon disintegrates."

This communication is based upon 518 cases over a period of 26 years. In 7 cases, the spinal supportive graft or grafts have been supplemented by a costal pelvis prop. The anterior end of the tenth rib has been selected as the point at which to affix the tibial graft. These ribs, rather than one of the lower ones, have been selected because they are more firmly anchored to the thoracic cage and will therefore transmit the corrective influence directly to the spine. X-ray films of cases taken over 20 years after operation disclose that grafts maintain their conformation and do not yield to the extensive pressure which they have often withstood for so long a time. Even after many years their stabilizing and corrective influence continues.

SUMMARY

The bone graft is of the greatest aid to the surgeon in the following manner:

1. The leverage and splintage action of the graft is exerted directly upon the vertebræ themselves at the curvature.
2. The graft is subject to a favorable stress in scoliosis and exhibits remarkable hypertrophy.
3. The graft lends itself to x-ray study in establishing progress and permanency of fusion.
4. The graft adds more bone when it is urgently needed; the bone in the spinous processes of thoracic region of spine is insufficient.
5. The graft brings a rapid callus producing bone into a low osteogenetic area.
6. Fusion after the curve is opened up or partially straightened often increases the height of the patient by several inches.

REFERENCES

1. Albee, Fred H. Orthopedic and Reconstruction Surgery. Philadelphia: W. B. Saunders Company, 1921.
2. Idem. The bone graft operation for tuberculosis of the spine. J. Am. M. Ass., 1930, 94: 1487.
3. Idem. Spinal tuberculosis, climatic and operative treatment. Am. J. Surg., 1935, 30: 60.
4. Brogden, W. E. J. Bone & Joint Surg., 1936, 18: 1027.
5. Gaenslen, W. F. J. Am. M. Ass., 1923, 81: 1578.
6. Preston, Robert L. Scoliosis. Internat. Abst. Surg., 1934, 59: 1.
7. Steindler, A. Diseases and Deformities of Spine and Thorax. St. Louis: C. V. Mosby Company, 1929.
8. Idem. Mechanics of Normal and Pathological Locomotion of Man. Springfield, Ill.: C. C. Thomas, 1935.
9. Whitman, R. J. Am. M. Ass., 1936, 106: 112.

PRIMARY FIBROBLASTIC TUMORS OF THE CHOROID PLEXUS OF THE LATERAL VENTRICLES

A Clinicopathological Study of Three Cases

W. JAMES GARDNER, M.D., and OSCAR A. TURNER, M.D., Cleveland, Ohio

PRIMARY benign intraventricular tumors are uncommon and, with few exceptions, the literature consists of scattered reports of single cases. Dandy (4) states that they constitute about 0.75 per cent of all brain tumors. While this number is exceedingly small, certain clinical and pathological findings related to these tumors make them of interest.

The recognition of primary benign intraventricular tumors by clinical means is practically impossible. Usually associated with marked increase of intracranial pressure, these tumors produce signs which, as a group, point to no specific area of the brain but may occasionally cause neurological changes which direct attention to several widely separated cerebral areas. Thus, the symptoms and signs are apt to be quite confusing. However, with the advent of pneumographic studies as an aid to the localization of intracranial growths, the absence of localizing phenomena has come to be of less serious consequence than formerly.

From the standpoint of the bio-history and histological character of the tumors, the prognosis for the patient is excellent, but the large size which these tumors attain and the trauma which is concomitant with their removal makes this a hazardous procedure. The study of the pathology of this group of tumors has been neglected to a great degree. As Davis and Cushing have stated, there is a tendency in the literature to describe in one category a great variety of lesions which protrude into the ventricle and to assume, without accurate histological evidence, that they actually have originated from the adjacent plexus.

The 3 following cases are of interest both from the clinical and pathological standpoints. The diagnostic difficulties have already been referred to and the fact that all three tumors are primary fibroblastomas which arose, without reasonable doubt, from the choroid plexus or tela choroidea makes them worthy of consideration.

From the Cleveland Clinic.
Presented before the Cleveland Neurological Society, Canton, Ohio, May 26, 1937.

REPORT OF CASES

CASE 1. The patient, a 36 year old white man, entered the hospital in September, 1927, complaining of severe headaches, nervousness, loss of memory and staggering gait. About 6 weeks before admission he had experienced a severe headache which had lasted for about 6 hours. Two weeks later he had an attack of faintness which had lasted but a few minutes. Following these episodes he became very nervous, some unsteadiness in walking developed, and he had "lost confidence in himself." Drowsiness had been present since the beginning of the year, but there had been no nausea or vomiting. For 3 weeks previous to admission the patient had himself noticed a failing memory and, for the past 10 days, the headache which had been most marked over the vertex had become almost constant. No history of failing vision, sensory, or motor defect was elicited nor had there been diplopia or tinnitus.

Neurological examination revealed little at that time. There was a slight bilateral exophthalmos, some decreased auditory acuity on the right side, and a slight amount of ataxia. Motor and sensory defects were absent. The optic discs appeared normal. Subjectively, there was a loss of memory and some dizziness. A regimen for the administration of luminal was instituted and the patient was told to report at regular intervals for further observation.

Repeated spinal punctures during the subsequent interval revealed normal fluid dynamics but some xanthochromia. However, after 2 months the patient began to show definite signs of an expanding intracranial lesion. He was found to be mentally dull and he had almost total motor aphasia. There was slight edema of both optic discs, but definite choking was absent; bilateral exophthalmos was present. Marked hypertonicity was present over the entire right side and the Babinski sign was present bilaterally. There had been a transient paralysis of the right lower part of the face and the headaches had become more severe.

In November, 1927, in the hope of finding a removable growth, an osteoplastic flap was reflected in the left temporoparietal region. The exploring brain cannula localized a deep seated tumor. The wound was closed leaving a decompression without an attempt at removal of growth. After a somewhat stormy course, patient was discharged with little improvement over his former condition. Subsequent therapy with filtered x-rays was followed by considerable improvement and he was practically symptom-free up to the time of the second admission in July, 1930—32 months after operation.

Two days previous to the second admission the patient had experienced a generalized convulsion in his sleep but, aside from a rather sluggish mentality and a slightly drawling speech, there was nothing to suggest a cerebral lesion. Encephalography was advised in the hope of localizing a cyst which could be drained. Roentgen examination (Fig. 1) gave evidence of a large tumor obstructing the posterior portion of the body of the ventricle in the left occipitoparietal region.

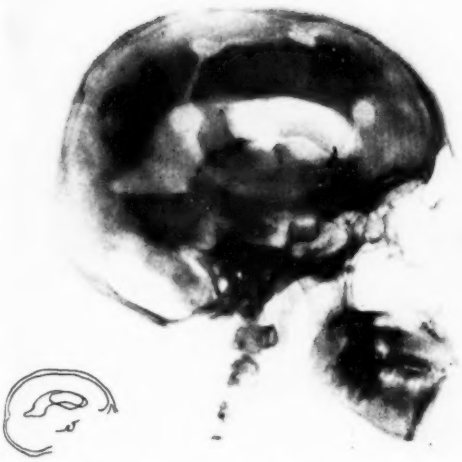


Fig. 1. Encephalogram. The outlines of the previous bone flap and decompression are evident. There is dilatation of the right ventricle. The left ventricle is obstructed so that only the anterior half of the body is visualized. Case 1.

Under avertin ether anesthesia, a left occipital craniotomy was performed. Cannula exploration yielded 3 to 4 cubic centimeters of yellow coagulable fluid at a depth of about 3 centimeters. An incision into the cortex exposed an encapsulated tumor which apparently was confined to the posterior portion of the left ventricle. An immediate biopsy was reported as possibly a fibroblastoma. Since piece-meal removal with the electric loop caused marked bleeding, the growth was removed by finger-enucleation after a preliminary transfusion. The tumor came away in two pieces and this was followed by sharp bleeding from its anterior attachment which was well forward on the mesial wall of the lateral ventricle. The anterior limit of the growth was almost as far forward as the foramen of Monro. This anterior portion was much more firm and much more nodular than the posterior portion and was thought to be the older part of the neoplasm.

Although the immediate response after operation was surprisingly good, the subsequent course was consistently downhill. An encephalogram made 10 days after operation showed that the symmetry of the ventricles was restored and there was no evidence of a clot. The patient died 5 weeks after operation. No autopsy was granted.

Pathological description. The total weight of the tumor was 135 grams. The largest piece measured approximately 6 by 5 by 5 centimeters and was grayish-white, soft, and rather friable. A scanty capsule covered the surface. The cut surface appeared slightly granular and without whorl formation. A smaller piece was somewhat firmer and rather nodular, but differed in no significant way from the above.

Sections of the tumor were stained with hematoxylin and eosin, Mallory's phosphotungstic acid hematoxylin, Weigert's resorcin-fuchsin for elastic tissue, Wilder's silver impregnation for reticulum, Mallory's anilin blue, orange G, acid fuchsin, and Perdrau's silver impregnation for connective tissue. Poor staining quality interfered to some extent with the histological examination of the specimen.

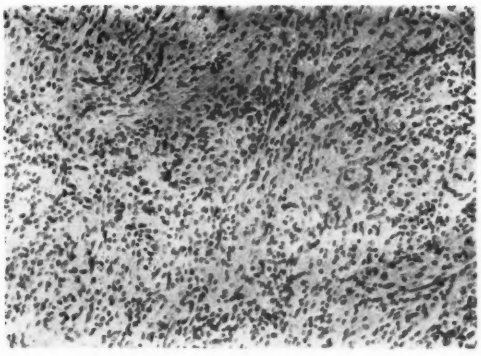


Fig. 2. Section of tumor. Note the indefinite cell boundaries and the abundance of intercellular collagenous material. Case 1. (Hematoxylin and eosin, x 120).

Microscopically, there is present a rather thin capsule composed of moderately dense collagenous connective tissue containing numerous small, thin walled vessels. The tumor tissue is quite cellular and with some disposition toward whorl formation, although this is not marked in all parts of the tumor. The individual cells have moderately small, round or oval, vacuolated nuclei which contain a relatively small amount of chromatin material in the form of coarse granules. Several nucleoli are usually present and the nuclear membrane is fairly distinct. There is a fair amount of finely granular cytoplasm which tends to be bipolar in distribution, although cytoplasmic boundaries are quite indistinct and often invisible. Intercellular material is quite abundant and, although the tumor appears densely fibrous, a definite reticulum is not present (Fig. 2). However, about the vessels in the immediate surrounding tumor tissue, there are small collections of fine fibrils which appear to have their origin from the vessel walls. There are numerous thin walled vessels and occasional large vessels, both of which are filled with moderately well preserved blood.

Where whorl formation is marked, hyalinization is often present and a few well formed calcospheres are evident. Fibroglia fibers were not demonstrated by the special stains although it is possible that the poor state of preservation of the tissue interfered with the staining of these. Pleomorphism is not marked, although occasional cells contain several nuclei and cells with large, round, swollen, atypical nuclei can be found. Scattered throughout the tissue are numerous round cells and in a few places these appear as focal collections. Areas of degeneration, although present, are not particularly common and not very extensive.

The tumor is regarded as a fibroblastoma.

Case 2. A patient, a 26 year old white man, was admitted to the hospital in May, 1932, complaining of ataxia, headaches, spontaneous vomiting, and drowsiness. The patient at the time of admission was stuporous and it was necessary to obtain most of the history from his wife.

Headache of mild severity had been present for 5 years. About 9 months prior to admission, the headaches had increased in severity and spontaneous vomiting had begun. For about 3 months the patient had complained of attacks of pain which were localized to the upper cervical region. These lasted from 15 minutes to 1 hour and necessitated sitting with the neck bowed and the chin resting on the

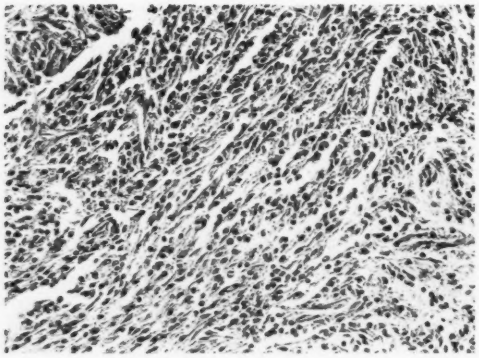


Fig. 3. Photomicrograph of tumor. Note evident fibroblastic character of the cells. Case 2. (Hematoxylin and eosin, x 187).

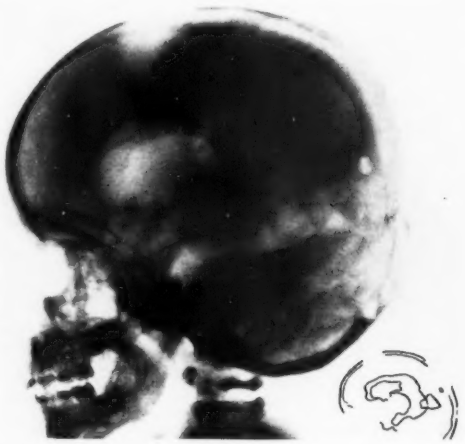


Fig. 4. Pre-operative ventriculogram. There is marked dilatation of the right ventricle. In the left ventricle there is an obstruction at about the midpoint of the body so that only the anterior portion and the occipital horn is visualized. Case 3.

sternum. About 6 weeks before admission the patient had been hospitalized elsewhere for observation, and at that time ataxia with staggering to the right had been noted. For 5 days prior to the first hospitalization there had been marked drowsiness, and regurgitation of food through the nose had prevented him from obtaining much nourishment.

Neurological examination gave definite evidence of an expanding intracranial growth, although localization was uncertain. There were bilateral choked discs with edema of one diopter on the right and two diopters on the left. The left pupil was fixed to light and although a definite nystagmus was absent, short nystagmoid jerks were present when the patient fixed the eyes to the left. A partial lower facial paralysis was present on the right and there was generalized muscular weakness most marked in the right arm and leg. Sensation was normal throughout. Ataxia was present and the Romberg test was positive, the tendency being to fall to the right. Moderate, bilateral adiadochocinesia was present also. The abdominal reflexes were absent and the gag reflex was impaired. The posture causing the patient the least discomfort was with the head bent forward and the chin resting on the chest. Perimetry could not be carried out. Roentgenograms of the skull gave evidence of long standing increased pressure. There was atrophy of the dorsum sella and clinoid processes with erosion of the floor of the sella turcica.

Ventriculograms taken on the third hospital day showed the air present only in the posterior portion of the right ventricle and this was dislocated to the right. The ventriculographic diagnosis was tumor of the left frontal lobe.

Left frontal craniotomy was performed following ventriculography. The exposed brain was tense but otherwise normal in appearance. Incision into the brain exposed the outer surface of a firm, encapsulated tumor confined within the anterior horn of the left lateral ventricle. After considerable difficulty the tumor was removed in two large pieces. Free bleeding occurred from the tumor bed, the blood coming from the vessels of the choroid plexus about the foramen of Monro.

Following a stormy postoperative course in which infection complicated recovery, the patient was discharged on the forty-fifth hospital day. He was re-admitted 2 months later complaining of drowsiness, weakness, and projectile vomiting. Neurologic examination was essentially negative, but in view of a previous infection and the presence of a high spinal fluid cell count, exploration for a cerebral abscess was carried out. No lesion was discovered and subsequent ventriculographic studies revealed nothing abnormal aside from the presence of a moderate dilatation of the ventricles. The patient was discharged on the seventh hospital day with considerable improvement in his condition. He died, however, 1 month later. No autopsy was granted.

Pathological description. The weight of the two large tumor masses was 190 grams. The larger measured 7 by 5.5 by 5.5 centimeters and, with the exception of one surface which was cut across in removal, the tumor was covered by a smooth, thin, glistening capsule in which numerous veins were visible. The surface was irregular with numerous large bosses. Sections through the tumor mass revealed a uniformly white, somewhat granular surface with numerous areas of recent hemorrhage. No cysts were present and gross calcification was not observed. The smaller mass weighed 45 grams and measured 4.5 by 4 by 3.5 centimeters. The tissue was similar to that of the larger mass but due to the presence of more diffuse hemorrhage its color was grayish red.

Tissue taken from various portions of the tumor was stained by the methods listed previously. Here again, the staining quality of the tissue interfered with the microscopic study of the growth.

Microscopically, there is a thin capsule composed of loosely woven connective tissue in which numerous large and small vessels are present. The cells are arranged in sheets and although the first impression is one of marked streaming and parallelism, close examination reveals the fact that this picture is due to the peculiar type of stroma present. The individual tumor cells are small, round, or elongated, and for the most part quite uniform. They contain one, but rarely two, small round, rather dense nuclei in which the chromatin material appears as coarse granules. The nucleus is usually centrally placed and in most instances occupies a large portion of the cell. The cytoplasm is moderate in amount and often appears as a small rim about the nucleus. It is finely granular and quite

Fig. 5. Photograph of tumor at operation. Case 3.

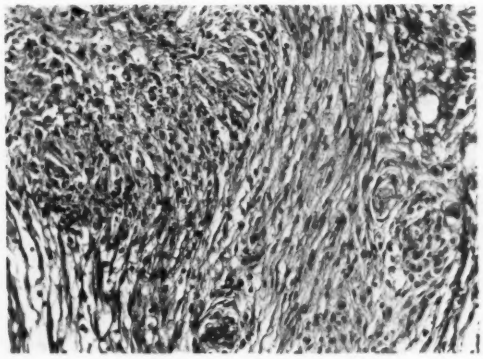


Fig. 6. Photomicrograph of tumor. Note the fibroblastic character of the tissue and the intimate relationship between tumor cells and blood vessels. Case 3. (Hematoxylin and eosin, x 105).

eosinophilic. Mitotic figures are present but not numerous. The tumor has an abundance of fine, collagenous stroma which supports numerous, fair size blood vessels. Specific stains fail to reveal fibroglia.

Degeneration is quite extensive and gives the tissue a loosely woven appearance. Definite whorl formation in the tumor is not present and streaming, although present, appears most marked where degeneration is present. In some areas the cells are in close contact to form sheets while in other places, streaming and parallelism predominates (Fig. 3). Extensive degeneration causes the tissue to appear under low magnification as focal cell collections separated by bands of fine collagenous connective tissue.

The tumor is regarded as a fibroblastoma.

Case 3. The patient, a 3½ year old white girl, entered the hospital in February, 1935, because of difficulty in the use of the right arm and leg. About 7 months prior to admission she had been knocked over by a dog and had fallen forcibly, but there was no history that she had struck her head. About that time the parents noticed a tremor in the right hand while the child was eating. Upon medical advice, she was put to bed for 1 week but upon getting up uncertain gait and marked difficulty in walking up and down stairs had been noticed. The child had become quite irritable and it was observed that the left hand was used much more than the right. There had been an increase of about 1 centimeter in the circumference of the head in the preceding 7 months. At no time had there been headaches or vomiting and speech had been normal.

Examination at the time of admission showed a bright child with a large head and an uncertain gait. The pupils were somewhat dilated but were equal and regular and responded normally to both light and distance. There was no nystagmus and the extra-ocular muscles were normal. Macewen's sign was positive. There was questionable slight weakness of the right lower portion of the face and the right hand, and definite ataxia of the right hand and leg. Deep and superficial reflexes were all active and equal but the Babinski response was present on the right. Both optic discs showed definite choking, and pressure over the left temple caused some pain. Perimetry was not carried out. The clinical diagnosis made was left frontal lobe tumor.

On the day following admission during the process of ventriculography a cyst was encountered through a drill opening in the left parietal region and about 30 cubic centimeters of thick yellow fluid was removed at a depth of about 4 to 5 centimeters. Following this procedure, air was introduced but from the subsequent films it was impossible to state whether the injected air outlined a cyst or an obstructed posterior horn of the left lateral ventricle. Consequently, 90 cubic centimeters of fluid from the right lateral ventricle was replaced with air and roentgenograms were made. These revealed a dilated right ventricle which was dislocated to the right and an obstruction at about the midpoint of the body of the left ventricle (Fig. 4). The diagnosis of left parieto-occipital cystic glioma was made and immediate operation performed.

Through a left parietal craniotomy opening, the brain was explored. The cerebral surface appeared normal with the exception of two gyri in the inferior portion of the parietal lobe. These were pale yellow, and soft, and, upon exploration with a biopsy cannula, increased resistance was encountered at a depth of about 5 centimeters. Several small fragments of tissue were removed with the cannula but because of the location and depth of the growth it was considered unwise to attempt its removal. The tissue removed proved to be normal brain tissue without evidence of inflammation or neoplasm.

The postoperative course was uneventful and the patient was discharged on the sixteenth day after operation. There was no measurable choking of the optic discs and the degree of ataxia was decidedly less than at the time of admission. Roentgentherapy was instituted and the child continued to make good progress until about 2 months after discharge, at which time she suffered from an illness in which vomiting was a prominent feature. Following this episode the use of the right side was definitely impaired. Symptoms of pressure developed gradually until, in November, 1935, 10 months after the first admission, the patient was readmitted for aspiration of the cyst. About 100 cubic centimeters of syrupy, yellow fluid was removed with subsequent improvement in the child's condition. In January, 1936, it was necessary again to aspirate fluid. At this time the child had complained twice of headache, and spontaneous vomiting had been present. One hundred cubic centimeters of fluid was removed but with much less improvement than was formerly obtained. The subsequent course was down-hill and in March, 1936, it became apparent that radical operation was the only measure which could

possibly save the child. At this time, there was a high degree of papilledema, marked ataxia, and separation of the cranial sutures.

Through a craniotomy opening corresponding to that of the previous operation, the left parietal region of the brain was again exposed. An incision through the cortex disclosed a collection of 6 or 8 cysts, all of which were located in a greatly dilated posterior horn of the ventricle. Evacuation of these brought to view a large, firm, smooth, encapsulated tumor lying anteriorly (Fig. 5). With the electrosurgical loop the tumor was removed piecemeal until there remained only a small portion of its anterior wall which was found to be attached to the choroid plexus at a point opposite a greatly dilated foramen of Monro. The vessels of the choroid plexus were greatly dilated and represented the only point of attachment of the growth. After coagulation of these it was possible to remove the last fragment of tumor tissue. An enormous cavity resulted, the walls of which consisted of the ependymal lining of a greatly dilated lateral ventricle. The cavity was filled with saline and the wound was closed in the usual manner.

The subsequent course was uneventful and the patient left the hospital on the eighteenth day after operation. At the time of discharge, there was some residual paresis and ataxia of the right side, but not demonstrable aphasia. Nine months after operation the patient was able to run and walk alone. She was able to use the right arm and leg and her condition had continued to improve steadily. However, there was still a definite right hemiparesis.

Pathological description. The total amount of tumor tissue removed weighed 217 grams. The largest piece measured 4.5 by 4.5 by 3 centimeters and was covered on its outer surface by a thick, yellowish gray to grayish white capsule. At one point, a fragment of choroid plexus was attached to the surface. The tissue was quite firm and upon section presented a homogeneous, yellowish gray, somewhat granular surface.

Sections taken from various parts of the tumor were stained by the methods already enumerated. The tumor is covered with a moderately thick capsule consisting of fairly cellular collagenous connective tissue in which numerous large and medium sized blood vessels are present. The tissue is composed of sheets of cells of the connective tissue type with fairly marked streaming and somewhat less marked whorl formation. Degeneration is extensive throughout the tissue.

The parenchymal cells are fibroblasts with elongated, compact, and highly chromophilic nuclei and a fair amount of pink-staining cytoplasm which is bipolar in distribution (Fig. 6). Intercellular material is abundant and forms a heavy collagenous carpet. Mitotic figures are not commonly found. Vessel spaces are quite numerous and about these there is some tendency for whorl formation with an intimate relationship existing between the walls of the vessel and the surrounding tumor tissue.

Although not very abundant, there are isolated areas in which fibroglia fibrils can be seen. Scattered here and there throughout the tissue are small, focal collections of hyperplastic epithelium derived from the choroid plexus. These have round, vacuolated, centrally placed nuclei and a small amount of very lightly staining cytoplasm with almost no definition of cell boundaries. No reticulum could be demonstrated in the tumor tissue, either with the Wilder or Perdrau method, although the latter demonstrated beautifully the abundant intercellular collagenous stroma. Sections taken at a point corresponding to the choroidal tissue seen on the gross specimen reveal the presence of numerous villi containing large and small vessels with thin, poorly formed walls.

The tumor is regarded as a typical fibroblastoma.

CLINICAL CONSIDERATIONS

Although the incidence of tumors of the lateral ventricle is relatively low, they arise often enough in neurosurgical practice to make their clinical consideration of value. There is no clinical picture which will localize an intraventricular growth although there are certain neurological features which may at times direct attention to the possibility of a lesion in this location. This is particularly true when localizing signs are absent in the presence of an obviously expanding intracranial lesion.

Periodic headaches or intermittent attacks of increased intracranial pressure have both been cited as the most suggestive evidence of a growth within the lateral ventricle (5). This periodicity is due to the ball-valve action of the tumor and can occur in other parts of the ventricular system, namely in the third ventricle (6). When the large size of the tumor prevents it from moving freely or when local adhesions fix the tumor in one position, this phenomenon may be absent as it was in the 3 cases presented here. Obvious signs of increased intracranial pressure may be late in developing in patients of the younger age group since here cranial suture separation may serve to decompress the brain until the bulk of the tumor plus the concomitant cerebral edema overcomes this compensation. Of the host of signs and symptoms described, hemianesthesia and hemiplegia have been pointed out as the most important localizing evidence. This is interesting in view of the fact that in none of the 3 cases described here was there any evidence of sensory impairment. Many of the signs are misleading and in one instance, at least, the presence of staggering gait, ataxia, and positive Romberg's sign has led to cerebellar exploration (7).

Intraventricular tumors appear to occur most frequently during the first three decades of life. Dandy (5) found that in about 67 per cent of the cases of tumor of the lateral ventricle, the patients were less than 31 years of age at the time of operation or necropsy and that nearly 50 per cent of these tumors occurred before the age of 21 years. Van Wagenen has reported the successful removal of a papilloma of the choroid plexus from the lateral ventricle of an infant 3 months old, and Graves and Fliess report the occurrence of a similar tumor, found at autopsy, in the left lateral ventricle of an infant 9 months old. Tchernyscheff and his associates have reported a psammoma which was located in the right lateral ventricle of a boy 10 years old and Christophe has reported a similar tumor which was found in a boy 13½ years old.

While in many instances the symptoms are less than 1 year in duration there are wide variations. The successful removal of an intraventricular tumor from a patient in whom symptoms had been present for 22 years has been reported (10). It must be remembered that, in tumors in this location, the duration of symptoms is no index of the malignancy of the growth since, by reason of their location, they may block circulation of the cerebrospinal fluid and produce fulminating signs of increased intracranial pressure, despite the fact that they may be encapsulated and perfectly benign.

PATHOLOGICAL CONSIDERATION

Tumors arising from the choroid villi have been described and usually referred to as psammomas (3, 11) or meningiomas (8). Although the microscopic structure of these tumors is variable, many of them cannot be distinguished from the common variety of meningioma. The tumors described here differ from the common variety of meningioma and, for reasons to be discussed, have been called fibroblastomas.

As has been pointed out elsewhere (2) cerebral neoplasms composed almost exclusively of fibroblastic elements are extremely uncommon. Their origin has not yet been definitely established, although Alpers has stated that these tumors may arise from the pia, the vascular adventitia, or the perithelium of the blood vessels. Inasmuch as the embryological derivation of the leptomeninges is still the subject of considerable debate, the term fibroblastoma eventually may prove to be incorrect.

There are several reasons for believing that the tumors described here arose from the mesodermal elements of the choroid plexus. Collagen fibrils, fibroglia fibrils, and elastic fibers are known to be the products of cells potentially fibroblastic. The first tumor described is densely fibrous and quite cellular and contains considerable intercellular collagenous material. In the third tumor, in addition to an abundant collagenous stroma and numerous fibroblasts, there are scattered areas in which fibroglia fibrils are present. While the fibroblastic character of the second tumor cannot be established definitely it appears that all three tumors are fibroblastomas. None of the tumors contained a definite reticulum. The three tumors described here probably arose from the fibrous elements of the choroid plexus, either from the numerous fibroblasts found normally in the choroidal villi or from cells potentially fibroblastic.

SUMMARY

1. Three cases of primary fibroblastoma of the choroid plexus of the lateral ventricle have been described. All 3 tumors were removed at operation.

2. In none of the 3 cases was the intraventricular location of the tumor suspected from the clinical findings and in all 3 cases the exact localization was made at operation.

3. The tumors are of mesodermal origin and probably arose from the fibrous elements of the choroid plexus or tela choroidea.

REFERENCES

1. Alpers, B. J., Yaskin, J. C., and Grant, F. C. Primary fibroblastoma of brain. Arch. Neurol. & Psychiat., 1932, 27: 270–281.
2. Baker, A. B., and Adams, J. M. Primary fibroblastoma of the brain. Am. J. Path., 1937, 13: 129–137.
3. Christophe, D., Divry, P., and Moreau. A case of psammoma of the choroid plexus of the lateral ventricle. J. belge de neurol. et de psychiat., 1934, 34: 733–738.
4. Dandy, W. E. Benign encapsulated tumors in lateral ventricles of brain; diagnosis and treatment. Ann. Surg., 1933, 98: 841–845.
5. Idem. Benign, Encapsulated Tumors in the Lateral Ventricles of the Brain. Baltimore: Williams & Wilkins Co., 1934.
6. Idem. Benign Tumors in the Third Ventricle of the Brain. Baltimore: C. C. Thomas, 1933.
7. Davis, L. E., and Cushing, H. Papillomas of choroid plexus. Arch. Neurol. & Psychiat., 1925, 13: 681–710.
8. Fincher, E. F. Intraventricular tumors of cerebrum; study of eight cases, including two lateral ventricle meningiomas. South. M. J., 1934, 27: 667–676.
9. Graves, G. W., and Fliess, M. M. Neoplasm of choroid plexus. Am. J. Dis. Child., 1934, 47: 97–103.
10. Lynn-Thomas, J. Epilepsy of 22 years' standing due to calcified endothelioma or perithelioma in left lateral ventricle; removal and recovery. Brit. J. Surg., 1922, 9: 490–494.
11. Tchernyscheff, A., Kopylow, M., and Terian, K. A case of choroid plexus psammoma in the right lateral ventricle. Ztschr. f. d. ges. Neurol. u. Psychiat., 1930, 129: 713–723.
12. Van Wagenen, W. P. Papillomas of choroid plexus. Arch. Surg., 1930, 20:199–231.

EPIDERMOID CARCINOMA OF THE BUCCAL MUCOSA

CHARLES C. LUND, M.D., F.A.C.S., Boston, Massachusetts

BUCCAL cancer is typically an epidermoid cancer and typically very malignant. The results of treatment by any means, surgery, radium, or x-ray, cannot by any criteria be considered to be at all satisfactory except in a very few, very small cancers and a few others that are of a relatively low grade of malignancy (4). Most of the few cases that are amenable to cure are curable by any of the aforementioned forms of treatment properly given. This situation does not prevail with respect to any other form of cancer except that arising in the skin or on the lips. Of course, in the latter two locations the cancers are much more frequently curable. This paper will discuss epidermoid cancer only, of the following locations; tongue, floor of mouth, upper and lower gingival mucosa, both palates and inside of cheeks. Notice that cancers of the tonsil and lips are not included and that the very rare adenocarcinomas and the so called lympho-epithelioma are not included. The characteristics of these other types and locations of cancer are so different that a wholly separate paper would be needed to discuss them in any worth while manner.

CAUSE AND PREVENTION OF BUCCAL CANCER

Normally the mucous membrane of the mouth is comparatively resistant to the development of cancer, as shown by the fact that women, who very largely do not chew tobacco or smoke pipes, and whose mouths average much cleaner in other ways than men's do, have buccal cancer but one-eighth as frequently as men (2). This statement holds approximately true for Europe, America, and many other parts of the world, but not for countries where betel nut chewing is commonly practiced by both sexes. The etiological factors well recognized to be causative of mouth cancer are: first, overuse of the stronger forms of tobacco such as, in order, chewing, either plain tobacco or snuff, pipe smoking, and cigar smoking; second, dirty, broken, infected teeth; third, important for some unknown reason in tongue cases only, tertiary syphilis. In most cases of buccal cancer at least two of these factors are present and have been operating over a long period of time. It is unfortunate that the irritative factor that leads to mouth cancer does irreversible damage to the tissues long before any visible effect takes place. This of course is similar to the effect of x-ray or the various tar chemicals, whose effects may be demonstrated only following a long latent period, but if sufficient dosage has been given will be shown eventually even if further administration of the agent be stopped.

This is mentioned because in this disease even more than in most diseases the prevention of it is better than the cure and it can be largely prevented. How far should one go in recommending preventive measures? Should we advise the confirmed pipe smoker to give up his pipe? I am afraid such advice would go unheeded. Notice that two or more of the causative factors are nearly always needed to cause this kind of cancer. Therefore, it would be fairly safe for the young man about to begin to enjoy adult pleasures to follow these rules: (1) avoid syphilis, or if an accident has happened, be treated efficiently; (2) either do not use tobacco, or keep the teeth, with the help of a dentist, in perfect order at all times.

THE SELECTION OF PATIENTS FOR CURATIVE TREATMENT

As with other kinds of cancer the patients must be sharply divided into two classes: (1) those in whom an attempt will be made to cure; (2) those in whom palliation only will be attempted. Ill advised attempts to cure will often result in excessive suffering and will even prevent effective palliation. The converse use of palliative measures when curative methods are indicated leads to an even more tragic result. Except for the occasional patient who has serious complicating disease or is very feeble from old age, no wide search has to be made before deciding on the curability of the cancer. No x-ray pictures are indicated to hunt for metastases, as the disease practically never shows metastases below the clavicle except in such a late stage that local cure is impossible. When, however, a cancer is adherent to the upper or lower jaw, x-ray examination of this one bone is indicated to demonstrate the amount of direct extension.

Except as indicated herein the decision as to curability of the individual case is determined

From the Cancer Commission of Harvard University.
Read before the section meeting of the American College of Surgeons, Halifax, Nova Scotia, May 21, 1937.

by (1) inspection and palpation of the tumor; (2) palpation of the lymph nodes in the neck; (3) biopsy of the tumor. The findings of each of these examinations should be known before treatment is decided upon. Biopsy tissue can be taken from the ulcerated surface of the tumor with a punch; this step should be a simple one and should not cause pain or danger to the patient. The report of the pathological examination must go further than merely state the presence or non-presence of cancer. It should, if an epidermoid carcinoma, give information as to the index of malignancy according to Broders or some similar classification.

An attempt at cure should be made in cases in which the largest lymph node is 1 centimeter or less, and in which the tumor is not over 2 centimeters in diameter, if of pathological grades 2 or 3 and also if the tumor is wider than 2 centimeters, but not over 4 centimeters provided the lesion is of papillary type, does not infiltrate, and is of pathological grade 1.

THE PREPARATION OF THE PATIENT FOR CURATIVE TREATMENT

Good hygiene of the mouth must be achieved before starting any course of curative treatment. In more cases this will entail extensive extractions than it will entail mere cleaning and temporary filling of teeth. This takes time, but it is believed to be so important that up to a week or 10 days for the extractions and partial healing of the sockets may well be spent in this effort before operation or radiation. Many serious post-treatment infections are thereby avoided and no appreciable increase in the size of the tumors have been noted during this time.

THE CURATIVE TREATMENT OF THE LOCAL LESION

The results of treatment by modern methods are very close to each other. A clean surgical excision by endothermy probably gives the least painful convalescence. We tend to favor this method especially if there is associated leucoplacia, as the latter does not respond well to radiation. A proper surgical endothermy or surgical excision operation should excise or devitalize the normal tissue to a distance of at least ½ centimeter in all directions beyond the edge of the gross cancer, and if possible, 1 centimeter distance is better. Endothermy combined with surgical excision is absolutely the method of choice if there is invasion of the jaw. A wide resection of the jaw will be followed by cure in many such cases. In an increasing number of the curable cases, however, the treatment starts with a series of 2000 to 3000 r units of short wave x-ray, given through the skin or 1500 units intra-orally if the tumor is so located that this is feasible. When this treatment is started, no change is ever made to surgery later. Three weeks after the first treatment the situation is reconsidered and further treatment given by either more x-ray or by the implantation of radium needles. A third series of treatments is given by x-ray at the end of a second 3 weeks when the dose is pushed to the limit of tolerance of the skin, the underlying tissues, and the patient. This is not necessarily the only way to give x-ray. Berven, of Stockholm, favors daily doses for 1 month, totalling 5000–6000 r units. If, after this treatment, the tumor has not regressed or, if after regression it recurs, no further effort is made to cure. After several months a few hundred, but only a few hundred, r units may be tolerated for palliative purposes.

TABLE I.—CLINICAL VERSUS PATHOLOGICAL EXAMINATION OF NODES OF NECK

Pre-operative diagnosis	Per cent correct	Pre-operative size cm.	Per cent involved
Positive	54	1.0 or less	48
Negative	65	1.1 or over	100

THE CURATIVE TREATMENT OF INVOLVED GLANDS IN THE NECK

It is often impossible to tell by clinical examination whether glands palpated in the neck are actually involved by cancer or not. There are two reasons for this. First, very small, impalpable glands may have a small cluster of cancer cells in them. Second, due to the infection of the teeth or the secondary infection of the ulcerated primary cancer the glands may be considerably enlarged due to their reaction to the infection, and yet contain no cancer cells. It goes without saying that really large glands practically always do contain metastases. Table I will show the difficulty of telling by any criteria on physical examination whether nodes are involved or not.

The data on comparison of the examiner's opinion as to the presence of cancer in the neck are from the paper by Simmons published in 1930, and the data on the described size, from reference Lund (4).

It is generally recognized that any feasible dosage of x-ray or external radium will very rarely cure metastatic epidermoid carcinoma in glands, and that the cure of such glands by implanted radium is extremely unlikely due to the

TABLE II.—CURE OF CASES BY RADICAL OPERATION

	Cases	5 year cures	Per cent
Glands positive	16	3	19
Glands negative	17	5	29

Quoted from previous article (4).

TABLE III.—RELATION OF GRADE AND SIZE TO GLANDULAR METASTASIS

Size of lesion cm.	Grade I		Grade II		Grade III		Total	
	Cases	No glands per cent	Cases	No glands per cent	Cases	No glands per cent	Cases	No glands per cent
0–1.0	3	100	2	50	3	33	8	63
1.1–2.0	9	67	17	35	12	17	38	37
2.1	17	71	23	13	14	0	54	28
Total	29	72	42	24	29	11	100	34

TABLE IV.—EPIDERMOID CARCINOMA OF THE BUCCAL MUCOSA

Location	Cases	No glands—per cent
Palate	3	100
Upper jaw	8	50
Floor	11	45
Cheek	16	38
Tongue	46	26
Lower jaw	16	25
Total	100	34

TABLE V.—519 PRIMARY CASES, SMALL GLANDS

Size—cm.	Cases	"Cures"	Per cent
0–1.0	30	13	43
1.1–2.0	103	19	18
2.1+	386	22	6
Total	519	54	11

difficulty of securing curative dosage in all the glands that may be involved. For these reasons one must state positively that if a patient has cancer in the glands his only important chance of cure is by surgery. What is this chance? In a previous paper (4), the results of radical operations on 33 such patients were reported. Radical operation is defined as an adequate local excision by knife, cautery, or endothermy, plus a neck dissection which includes the removal, on one side, of the submaxillary gland, submental gland, the greater portion of the sternomastoid muscle and of the internal jugular vein, together with all the gland bearing tissue from the clavicle to the jaw. The results following this operation are given in Table II. This table includes only cases in which the pre-operative description of the glands was given as small or not over 1 centimeter in diameter. In 7 other cases with larger glands none resulted in a 5 year cure.

Table II shows that it is possible to cure by surgery patients with buccal cancer who have small cervical metastases. Therefore, if the patient is otherwise curable and the glands are thought to be involved a radical neck dissection should be done, whether the primary lesion is irradiated or excised. This dissection should be done before, rather than after, radiation treatment as in most instances of radiation to buccal cancer the tissues of the upper neck will be so seriously damaged by the radiation that fatal infection is not unlikely to occur after operative procedure.

If I should be asked whether we always do such neck dissections in favorable cases (as described herein) the answer would have to be no. What defense is there for not doing them in view of the data presented as the impossibility of telling from the examination of the neck as to the presence or absence of glands? Still other criteria have been used. These criteria concern the location, character, size, and pathological appearance of the primary tumor itself.

THE DETERMINATION OF CASES THAT WILL PROBABLY NOT HAVE INVOLVED NODES

Table III is constructed on the basis as to whether positive involvement of the nodes was found either at operation or developed so that it was obvious at any subsequent time. The operations were by no means always radical ones. The pathological grades were determined by Dr. C. C. Simmons. It is seen that the chance of gland metastasis is comparatively small in low grade tumors and also is small in very small tumors. Therefore, we believe that it is safe not to do a primary neck dissection if this combination is found.

As a matter of fact, unless there is evidence from the glands themselves we do not do such dissections if the tumor is either small or low grade. The "large" low grade tumors that are cured are nearly always those papillary ones that cannot be distinguished clinically from cases of papillary leucoplacia except on microscopic examination.

In other types of cancer the duration of the history of cancer has often been used as a criterion for doing non-radical surgery. In the mouth our histories are particularly unreliable as there is difficulty in knowing when actual cancer began in the presence of a patch of leucoplacia. It may be stated that duration as found expressed on our histories does not help us make this decision.

However, the location in the mouth is important. From the same paper quoted in Table III is found the data in Table IV.

It may be seen from Table IV that the danger of gland metastasis is distinctly less when the cancer arises elsewhere than on the tongue and lower jaw. Therefore, the location of the tumor must also be considered when a decision is made for or against active treatment of the lymph nodes.

RESULTS OF TREATMENT

In my previous paper (4), tables of results are given. They show as stated before that the form of treatment given (surgery or radium) is not so important as the choice of cases for treatment or the correctness of application of the particular treatment. In the great bulk of cases the results are discouraging. In cases with small or no enlargement of the lymph nodes the "cures" amount to only 11 per cent as seen in Table V. However, this table is not a fair statement of the results of curative treatment as at least half of the cases were incurable because of local extension of the disease and were given x-ray treatment for palliative purposes only.

Table V shows 3 things: first, the very small number of cases coming in when the lesion is small; second, the really good results obtained in these cases; and third, the nearly hopeless situation that is found in the more advanced cases.

SUMMARY AND CONCLUSIONS

1. Epidermoid carcinoma of the buccal mucosa in most cases is difficult to cure.

2. Very small, and pathologically low grade tumors are very susceptible to cure by proper application of any recognized method.

3. Therefore, there is a tremendously important field in relation to this kind of cancer: the education of the public and of the doctor in order to bring about better results.

4. The choice of treatment has been discussed.

REFERENCES

1. Broders, A. C. Squamous cell epithelioma of the lip. J. Am. M. Ass., 1920, 74: 656.
2. Lund, C. C. Second primary cancer in cases of cancer of the buccal mucosa. New England J. Med., 1933, 209: 1144–1152.
3. Idem. Pathology of carcinoma of the buccal mucosa in relation to results of treatment. New England J. Med., 1933, 209: 126–130.
4. Lund, C. C., and Holton, H. M. Carcinoma of the buccal mucosa. New England J. Med., 1933, 208: 775–780.
5. Simmons, C. C. Cancer of the buccal mucosa. Ann. Surg., 1930, 92: 681.

EDITORIALS

SURGERY
Gynecology and Obstetrics

FRANKLIN H. MARTIN, M.D.
Founder and Managing Editor
1905–1935

ALLEN B. KANAVEL, EDITOR

Associates
LOYAL DAVIS
SUMNER L. KOCH MICHAEL L. MASON

DONALD C. BALFOUR, *Associate, Editorial Staff*

APRIL, 1938

THE CHOICE OF SUTURES IN THE SURGERY OF THE LARGE INTESTINE

IN the current discussion as to whether resection of the large intestine should be done in one stage, or in several by some adaptation of the principle of Mikulicz, the significance of the method of suture employed seems not to be fully appreciated. This is of great importance because of certain conditions associated with the large intestine which do not obtain to the same degree in the small intestine.

Such are the infectiousness of its contents, the vulnerability of its blood supply, and the thinness of its walls. Minor soiling of the peritoneum by the contents of the stomach, duodenum, jejunum, or ileum, while to be avoided if possible, does not carry the grave danger of a spreading peritonitis as does a contamination from within the large bowel. Similarly, relatively gross interruption of the blood supply in the former where the anastomotic circulation is so profuse, has not the danger of causing necrosis that it has in the latter where the interruption of a single terminal vessel may at times lead to a localized ischemia at the suture line. Then too, the walls of the colon, particularly in the sacculi, are of a thinness which allows a smaller margin of safety as regards both the placing of the suture and its holding power.

It is apparent then that, although the large bowel seems to be a grosser structure than the small, the surgical manipulation of it requires a more rigorous technique. This may be on the one hand the abandonment of a suture method within the abdomen and the carrying out of a resection and anastomosis extraperitoneally as is the case with the Mikulicz principle, or, on the other hand, the refinement of the method of suture. Should the latter produce as good results as the former, then there would be no question in any one's mind as to its desirability.

That it can do so in the hands of those accustomed to the employment of the fine silk technique seems probable, while the attempt to do so with the relatively gross manipulations accompanying the use of catgut sutures seems improbable. The latter even in the finer sizes and with attached needles tends to tear as the running suture customarily employed is drawn taut, and the fault is intensified in the large sizes and with the threaded needle. In addition any type of aseptic or relatively aseptic form of anastomosis is dependent upon the accurate placement of multiple interrupted sutures and is well-nigh impossible to carry out in the large intestine with catgut. On the other hand, fine twisted silk mounted on an equally fine needle and used in interrupted stitches can be employed with great accuracy and with a minimum of damage to the wall of

the large intestine and its circulation. When perforations into the lumen occur, there is to a far lesser degree danger of serious leakage, while soiling of the peritoneal cavity during resection and anastomosis can be avoided by the use of an aseptic or relatively aseptic method of anastomosis which this refined technique permits.

From this consideration of the relative value of the resection and anastomosis according to the Mikulicz principle and that of resection and primary suture of the large intestine, it would seem that to those familiar with and experienced in the fine silk technique, the latter will be preferable, but that to those who for any reason persist in using catgut in the surgery of the large intestine, the Mikulicz procedure is the safer one.

SAMUEL C. HARVEY.

TREATMENT OF COMPOUND FRACTURES

THIS is not an extended treatise on the treatment of compound fractures but an attempt to emphasize three important points.

1. *Early attack.* Following the accident, the period in which it is possible, by débridement and thorough irrigation, to prevent infection is a limited one. Probably after 2 hours and surely after 4, the best we can hope for by such treatment is to limit the severity and the extent of the infection. Therefore, the operative attack should not be delayed, except for extreme shock.

2. *Early reduction.* After infection has developed it may be unwise to attempt a reduction of displacement of the fragments lest the infection be carried into areas as yet uninvaded. After the infection has subsided, new bone formation and the condition of the adjacent soft parts will usually prevent proper adjustment. The time to obtain satisfactory alinement is when the débridement is carried out. It is apt to be then or never. Surgeons are apt to wait for a better time to reduce the displacement. There is no better time than right away.

3. *Immobilization.* During the process of repair, it is of the greatest importance that the zone of infection be limited as much as possible. Any motion of the bone ends tends to tear the young granulation tissue and to break down the barriers of resistance. Traction and suspension alone do not provide sufficient immobilization. Circular plaster, even if carried well beyond the adjacent joints, is not always sufficient. This is especially true when a large window has to be cut in the plaster to allow treatment of the wound. Molded plaster gutters in connection with traction and suspension should be used more often than they are.

The use of internal fixation by screws and perhaps plates is often definitely indicated. In many comminuted cases it is the only way by which the proper length can be maintained. Their use in compound fractures frequently will limit the area of infection and hasten repair. They should be regarded as a temporary means of maintaining immobilization and should be applied in such a manner as to permit their removal with as little additional trauma as possible.

WILLIAM DARRACH.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

THE mortality of acute bowel obstruction has always been high when contrasted with statistics of other types of "acute abdomen." The death rate following operations to remedy the conditions is still inexcusable. Ignorance of the mechanism and effects of distention, of the mechanism of death, faulty diagnosis, late operation, and peritonitis resulting from the unskilled handling of distended bowel, are factors which contribute to this high mortality. Therefore, no treatise on the operative technique of bowel surgery is presented by Wangensteen in his recent book, *The Therapeutic Problem in Bowel Obstructions*[1] but rather an experimental and clinical study of the effects of obstruction, methods of diagnosis, and a description of conservative aids to recognized operative procedures.

This volume has three sections: (1) the therapeutic problem of acute bowel obstruction, an essay awarded the Gross prize in 1935; (2) general considerations of diagnosis and treatment in bowel obstructions; (3) the special obstructions. The following brief résumé contains facts which the reviewer believes worthy of special emphasis.

Obstruction produces distention and loss of fluid; the chief sources of distention are digestive fluids and swallowed air. Contrary to prevalent opinion, high obstruction is less vicious than blocks in the lower bowel, because vomiting prevents distention and attendant mechanical damage in the former type. Salt solution is a specific for the loss of electrolytes in high obstruction; it has no specific action in low obstruction. In obstructions of the colon, the latter becomes a closed loop, because of the action of the ileocecal valve. Vomiting is infrequent and normal absorption occurs. The danger lies in possibilities of damage to the colonic wall from a sustained enteric pressure, which may reach 24 centimeters of water. The cause of death in simple or non-strangulated obstructions of the small bowel, is not toxic absorption, but loss of viability and subsequent permeability of the bowel wall leading to peritonitis.

Criteria for the diagnosis of obstruction are thoroughly discussed. Roentgenographic findings are of value in determining the approximate level and degree of obstruction, as well as the efficacy of conservative decompression. The presence of peritoneal reaction is the important sign in differentiating simple, from strangulating, obstructions.

The therapy of bowel obstruction is summed up as follows: (1) saline solution, (2) blood transfusions, (3) decompression with inlying duodenal tube, (4) operation. Transfusion of blood is particularly indicated in strangulating obstructions because of blood loss in the mesentery and bowel of the obstructed segment.

Conservative decompression, concerning which the author has made numerous experimental and clinical contributions to the literature, is discussed at great length. A simple siphon device for maintaining suction is described. Criteria for determining the efficacy and limitations of suction are presented, as well as are the indications for surgery. Some cases, particularly those of partial obstruction, will be relieved by suction. Aseptic enterostomy, close to the obstruction level, is the safest procedure in late cases with great distention. Surgical attack is still our most important therapeutic agent and should be resorted to promptly when conservative decompression fails.

In the opinion of the reviewer, Wangensteen's work will long remain as the outstanding contribution to the treatment of acute obstruction. He has done a fascinating and intelligent piece of research. Could every doctor called upon to treat acute bowel obstruction be made to master the relatively few and simple concepts of the mechanism, diagnosis, and treatment of this catastrophe, as herein presented, the mortality would be reduced to a negligible percentage. J. R. BUCHBINDER.

[1] THE THERAPEUTIC PROBLEM IN BOWEL OBSTRUCTIONS; A PHYSIOLOGICAL AND CLINICAL CONSIDERATION. By Owen H. Wangensteen, B.A., M.D., Ph.D. Springfield, Ill. and Baltimore, Md.: Charles C. Thomas, 1937.

VOLUME 3 of *Post-graduate Surgery*,[2] the final volume, has been released and is comparable in every way to the two previously issued. This large volume consisting of about 2000 pages has many points of interest. One part consisting of 164 pages is devoted to the surgery of the vascular system. Of this, 56 pages are given over to a discussion of the surgery of the heart. This section is complete and contains all new material and is an excellent compilation of the data of the day pertaining to the subject. Probably the outstanding part of the volume is that devoted to the lymphatic system. As one surveys practically every text of surgery, definite information pertaining to the lymphatic system is either very brief or vague. Here is to be found a very comprehensive, yet concise, dissertation upon the subject. The material is prepared by several authors: three chapters by Rodney Maingot, an interesting chapter on Hodgkin's lymphogranuloma by Sir Humphrey Rolleston, and an impression of status thymo-lymphaticus by R. Sleigh Johnson.

[2] POST-GRADUATE SURGERY. Edited by Rodney Maingot, F.R.C.S. (Eng.). Vol. 3. New York: D. Appleton-Century Co., Inc., 1937.

The parts dealing with malignant tumors of the pharynx and larynx by Lionel Colledge; tongue, mouth, and lips by Stanford Cade; and the esophagus and diaphragm by Laurence O'Shaughnessy are deserving of special mention. It was a delight to read them.

Parts are devoted to the medical aspect of surgery, hernia, plastic surgery, obstetric surgery, orthopedics, eye, ear, nose, endoscopic methods, tonsils and adenoids and retropharyngeal abscess, mandible, teeth, venereal disease, physical medicine, deep X-ray therapy, some aspects of general surgery including shock, blood transfusion by the continuous drip method, gangrene, burns and the like, and some neurological and psychiatric aspects of surgery.

Because of lack of space it is impossible to give an adequate impression of the entire work. It is replete with vital information and a ready assistant to the student of surgery.

After having carefully surveyed the three volumes of *Post-graduate Surgery* an impression as to the merits of the system as a whole is volunteered. It consists of 5500 pages of material prepared by 59 authors, each a recognized master of his specialty. Much of the fundamental material depicting basic principles of surgery has been purposely omitted because the editor assumes that the post-graduate student should be in possession of this information and if not it can be procured in practically any textbook of surgery. Therefore the 5500 pages are devoted to what may be termed live clinical surgery. The presentation is excellent and the illustrations are numerous and beautifully done. Many subjects are treated exhaustively. The final opinion is that this work is probably the most complete and modern of any of its kind to be found today. The reviewer will cherish this system and use it frequently. In trying to offer a criticism, one fault may be found: a volume of 2000 pages is too large and heavy for convenient reading. JOHN A. WOLFER.

THE first part of the book *The Physiology of the Kidney*[1] by Homer W. Smith contains a good discussion of the physiological anatomy of the kidney and a review of the theories of renal function with some added recent concepts of the author. Smith has presented supportive experimental evidence for the theory of tubular excretion as seen in the aglomerular fish and embryonic preparations of lower animals.

The rôle of the kidney in mineral metabolism, acid-base balance, and water excretion is well handled from a practical standpoint, and helps to elucidate some of the problems and findings of advanced renal disease. The action of diuretics on the kidney is summarized.

Much of the book is devoted to the "concept of renal clearance." The clearance of inulin, phenol red creatine, urea and glucose is discussed thoroughly, involving technical detail and a thorough knowledge of biochemistry. The author believes that "independent absolute values of renal clearance are of little value" and, it is essential to observe the simultaneous clearance of two or more substances which we wish to compare.

It is unfortunate that the publishing of the book antedates the recent epoch making and generally accepted reports of the effect of renal ischemia. No mention of this work is made in the chapter devoted to renal blood flow.

The relationship of the kidney to the hypothalamus and adrenals is briefly discussed but the relationship of kidney and other organs such as heart, blood vessels, and liver are not elaborated upon.

As a whole the book is a scholarly presentation of the author's own experimental work on the physiology of the normal kidney of many laboratory animals. To this he has added an exhaustive review of the work of similar nature as initiated by Cushing and Richards.

It is a presentation written for those particularly interested in the subject of renal physiology, and not for the general practitioner. M. HERBERT BARBER.

ONE need only scan the contents of this the fifth edition of Ormsby's *Practical Treatise on Diseases of the Skin*[2] to discover why it has been so extremely popular. In order to incorporate new material and yet keep the book reasonable in size a great deal of reconstruction has been done. Twenty new diseases are described, descriptions of 12 have been rewritten, and the entire work has been brought up to date. The bibliography, always an excellent one in all of the editions, has been improved by selecting articles on the various subjects which contain bibliography to the date of publication, thus reducing the literature references.

The revision of the histopathology and mycology by Dr. Finnerud is an excellent piece of work and under each disease, a complete description of the histopathological findings is given in a short, concise, yet comprehensive manner.

The volume always has been well illustrated with excellent black and white engravings and to this volume are added 44 new plates. The subject matter is sound and presented in a direct, concise manner, reflecting the extensive knowledge and long teaching experience of the author. This book is the most readable, the most understandable, and the most authentic of all the textbooks on dermatology printed in the English language. It would be impossible to find a better book on the subject of dermatology in which every disease of the skin is so accurately described and in which everything known to date about any given disease is so ably presented.

The book is printed on good paper in clear, readable type, interspersed with bold type for key words and headings.

[1] THE PHYSIOLOGY OF THE KIDNEY. By Homer W. Smith, A.B., Sc.D., M.S.(Hon.). New York: Oxford University Press, 1937.

[2] A PRACTICAL TREATISE ON DISEASES OF THE SKIN; FOR THE USE OF STUDENTS AND PRACTITIONERS. By Oliver S. Ormsby, M.D. 5th rev. ed. Philadelphia: Lea & Febiger, 1937.

Needless to say, it is a pleasure to recommend this volume to all medical students and to all practitioners who are interested in the subject of dermatology and syphilis as an excellent work from which the medical student may grasp the fundamentals of dermatology and to which the practitioner may turn as a most valuable reference hand book.

E. A. Oliver.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

St. Thomas's Hospital Reports. Edited by Prof. O. L. V. S. De Wesselow, Mr. C. Max Page, assisted by Mr. N. R. Barrett, Dr. J. St. C. Elkington, Dr. A. J. Wrigley. 2d series —Vol. 2. London: St. Thomas's Hospital, 1937.

Physicians' Vitamin Reference Book. New York: E. R. Squibb & Sons, 1938.

J. B. Murphy; Stormy Petrel of Surgery. Loyal Davis, M.D. New York: G. P. Putnam's Sons, 1938.

The Diagnosis and Treatment of Diseases of the Blood. By Thomas Ordway, M.D., and L. Whittington Gorham, M.D. Revised by Raphael Isaacs, M.D. London, New York, and Toronto: Oxford University Press, 1937. (Reprinted from Oxford Monographs on Diagnosis and Treatment.)

X-Rays and Radium in the Treatment of Diseases of the Skin. By George M. MacKee, M.D. 3d rev. ed. Philadelphia: Lea & Febiger, 1938.

The Treatment of Clinical and Laboratory Data; an Introduction to Statistical Ideas and Methods for Medical and Dental Workers. By Donald Mainland, M.B., Ch.B., D.Sc. (Edin.). Edinburgh and London: Oliver and Boyd, 1938.

CORRESPONDENCE

THE FRANCIS AMORY SEPTENNIAL PRIZE OF THE AMERICAN ACADEMY OF ARTS AND SCIENCES

In compliance with the requirements of a gift under the will of the late Francis Amory of Beverly, Massachusetts, the American Academy of Arts and Sciences announces the offer of a septennial prize for outstanding work with reference to the alleviation or cure of diseases affecting the human genital organs, to be known as the Francis Amory Septennial Prize. The gift provides a fund, the income of which may be awarded for conspicuously meritorious contributions to the field of knowledge "during the said septennial period next preceding any award thereof, through experiment, study or otherwise . . . in the diseases of the human sexual generative organs in general." The prize may be awarded to any individual or individuals for work of "extraordinary or exceptional merit" in his field.

In case there is work of a quality to warrant it, the first award will be made in 1940. The total amount of the award will exceed ten thousand dollars, and may be given in one or more awards. It rests solely within the discretion of the Academy whether an award shall be made at the end of any given seven-year period, and also whether on any occasion the prize shall be awarded to more than a single individual.

While there will be no formal nominations, and no formal essays or treatises will be required, the Committee invites suggestions, which should be made to the Amory Fund Committee, care of the American Academy of Arts and Sciences, 28 Newbury Street, Boston, Massachusetts, U. S. A.